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*New and*  
*Nonofficial Remedies*  
**1948**



# New and Nonofficial Remedies ' 22 1948

Containing Descriptions of the Articles  
Which Stand Accepted by the Council on  
Pharmacy and Chemistry of the American  
Medical Association on June 15, 1948

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*Issued Under the Direction and Supervision of*  
the COUNCIL ON PHARMACY AND CHEMISTRY  
*of the AMERICAN MEDICAL ASSOCIATION*

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Philadelphia

London

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## Preface

This book is published under the direction and supervision of the Council on Pharmacy and Chemistry, which is a standing committee appointed by the Board of Trustees of the American Medical Association to consider medicinal and allied preparations offered by pharmaceutical and other manufacturers for prophylactic or therapeutic use by the physician. In it are listed and described articles which the Council has found acceptable up to June 15 of the year of publication. The book is constantly in review by the Council to eliminate preparations which have not lived up to their promise of value, and those which have been official for 20 years. Each year the general articles on the various classifications of preparations are reviewed to bring them up to date with current medical knowledge, such revisions being made by the action of the full Council. During the year descriptions of such other medicinal substances as are accepted by the Council for N.N.R. will be published from time to time in *The Journal* of the American Medical Association. The Council also is responsible for the publication of *Useful Drugs, the Epitome of the Pharmacopeia of the United States and National Formulary*, the *Annual Reprints of Council Reports*, as well as articles and monographs on subjects of current interest to the medical profession which appear from time to time in *The Journal* of the American Medical Association.

The descriptions of accepted articles contained in this book are based in part on investigations made by, or under the direction of the Council and in part on evidence or information supplied by the manufacturer or his agents. Further explanations of the rules by which the Council proceeds in its deliberations may be found elsewhere in this book.

Nonproprietary or generic names are presented in the monograph headings in bold face capitals; protected names in bold face upper and lower case type. Chemical descriptions providing tests and standards for the uniformity of accepted articles have been grouped alphabetically in a section entitled "Tests and Standards."

In line with action taken by the Council during 1943, only the metric system is used in the publications for which the Council is responsible. Adequate conversion tables may be found in each publication for those who wish to convert other units into metric equivalents.

Criticism of *New and Nonofficial Remedies* is invited with a view to any further improvements of the book.

Acknowledgment is made of the technical editorial assistance of Bernard E. Conley, R.Ph., and of the help of others including Walton Van Winkle, Jr., M.D., Harold D. Kautz, M.D., Cecil C. Bean, M.A., and Diana Korkoneas of the Council office and of Albert E. Sidwell, Jr., Ph.D., Walter Wolman, Ph.D., Anna Louise Nestmann, M. Chem. and Anne Shimkus of the A. M. A. Chemical Laboratory.

AUSTIN SMITH, *Editor.*

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# Official Rules of the Council on Pharmacy and Chemistry

## INTRODUCTION

The Council on Pharmacy and Chemistry was created in 1905 as a standing committee appointed by the Board of Trustees of the American Medical Association.

*Activities of the Council.*—The Council publishes annually a book designated *New and Nonofficial Remedies* (N. N. R.), which contains a description of preparations and articles which have been examined and accepted by the Council for inclusion in that publication. The book provides statements on actions, uses, dosage, tests and standards of the preparations and articles. The book also contains certain official preparations and other articles, including drug substances for manufacturing use for which there are not official standards, which the Council is of the opinion should be included for the information of the medical profession.

The activities of the Council also include the preparation of special treatises, articles, status reports and books designed for the practitioner and the medical student, the giving of grants-in-aid for therapeutic research, the securing of therapeutic trial of promising new preparations and the encouragement of basic research on fundamental therapeutic problems.

*Acceptance of Articles for N. N. R.*—The principles and policies of the Council concerning the acceptance of a preparation or article for inclusion in *New and Nonofficial Remedies* are briefly expressed in the following rules:

### RULES GOVERNING THE ADMISSION OF ARTICLES TO THE BOOK "NEW AND NONOFFICIAL REMEDIES"

*Rule 1.*—COMPOSITION.—The quantitative composition of preparations and articles submitted to the Council or considered by the Council for inclusion in *New and Nonofficial Remedies* must be made known and may be published.

*Rule 2.*—IDENTIFICATION.—Suitable procedures and criteria for determining the composition or standardization of the submitted preparation or article must be furnished.

*Rule 3.*—ADVERTISING TO THE PUBLIC.—Preparations and articles promoted to the public for use in the treatment of disease will not be accepted except as specified in the explanatory comments.

*Rule 4.*—THERAPEUTIC CLAIMS.—When an article is accepted, therapeutic representations by the manufacturers or their agents

must be confined to those given in N. N. R. or accepted by the Council between revisions of N. N. R.

**Rule 5.—PROTECTED NAMES.**—Trademark names for medicinal articles are accepted if the Council deems the use of such protected names not to be harmful to health and if the common or generic names are not unduly subordinated to such trademarks in the labeling and advertising of the products.

**Rule 6.—PATENTS AND TRADEMARKS.**—If a preparation or product is patented as to process or product or both, the number of such patent or patents must be furnished to the Council. If the name of an article is registered or the label copyrighted, the registration (trademark) name and number and copies of the protected label must be furnished to the Council.

**Rule 7.—UNSCIENTIFIC AND USELESS ARTICLES.**—A preparation or an article will not be accepted if in the opinion of the Council it will not be in the best interests of rational medicine and the public.

#### EXPLANATORY COMMENTS ON THE RULES

**Rule 1.—COMPOSITION.**—*The quantitative composition of preparations and articles submitted to the Council or considered by the Council for inclusion in New and Nonofficial Remedies must be made known and may be published.*

**Secrecy Is Out of Place in Medicine.**—Intelligent prescribing requires that the physician have access to full information as to the composition of what he prescribes. An article cannot be accepted unless this information is furnished fully and truthfully. Information that is not available for publication at the discretion of the Council is of no service and will not be accepted.

**Statement of Composition.**—Drugs in interstate commerce must bear on their labeling a statement of composition under the Federal Food, Drug, and Cosmetic Act. Labeling of mixtures that do not come under this Act, such as those sold in intra-state commerce, must contain, if presented to the Council, a statement of the amount of each potent or important ingredient in a given quantity of the mixture. In the case of a *definite chemical substance or mixture*, a descriptive name satisfactory to the Council must appear on the labeling and in the advertising. If a name is unsatisfactory, the Council may propose a name.

**Vehicles and Preservatives.**—The general character of the vehicle and the identity of preservatives or of any other substance, whether added or present as an impurity, must be stated if these can under any circumstances affect the therapeutic action of the article. This does not mean the publication of the details of the working formula.

In the case of preparations for parenteral injection, the identity and amount of preservatives must be declared in the labeling, preferably on the individual container label but when this is im-

practicable, on the carton label or individual package insert; in the event that no preservative is present, the absence must be declared. The term "preservative" is intended to include all substances used for the purpose of preserving the identity, strength, quality or purity of a preparation. Thus, not only bactericidal or bacteriostatic agents are required to be declared in the labeling but other chemicals, such as stabilizers, anti-oxidants and buffers.

Preparations containing 1 per cent or more of benzyl alcohol must have this ingredient included as part of the name, as benzyl alcohol in such amounts acts as a local anesthetic and constitutes a potent therapeutic agent; for example, solution sodium morrhuate 5% with benzyl alcohol 2%.

The Council requires that chlorobutanol be included in the title of those preparations which contain more than 0.5 per cent of chlorobutanol unless the manufacturer can show evidence that the presence of this amount does not have therapeutic as well as antiseptic effect.

*Nonofficial Constituents.*—Nonofficial constituents of mixtures must be presented by the manufacturer in the regular way and must be acted on by the Council before the preparations containing them can be accepted.

Constituents that are not concerned in the pharmacologic action of the preparation need not be submitted in detail, but their nature and quantity must be disclosed to the Council so that it may be judged that they are inert. The Council may require that they be declared on the labeling by such designations as will make their nature or purpose apparent.

*Deliberate Misrepresentation.*—If it appears that a manufacturer has made a deliberately false statement concerning a product, he is asked to furnish an explanation, and if this is not satisfactory the product will not be accepted, even if the false statement is subsequently corrected or omitted.

*Testimonials.*—The foregoing paragraph applies not only to statements made to the Council but also to statements furnished to physicians by the manufacturer or his agents, even when these statements are in the form of testimonials.

*Inspection of Factories.*—The Council does not routinely accept invitations to inspect factories; its concern is with the finished products. If such action seems indicated, a representative may visit the factory or principal place of business and manufacture to obtain first-hand information concerning the manufacturing establishment, the facilities and controls available, the nature of the laboratory and experimental facilities operating in conjunction with the plant, and the scientific personnel and investigative projects.

**Rule 2.—IDENTIFICATION.**—*Suitable procedures and criteria for determining the composition or standardization of the submitted preparation or article must be furnished.*



The manufacturers of a drug should supply this information, which is necessary to control the quality of an article. For *chemical compounds* this should include tests for identity, amount and purity. In case of *mixtures*, methods for determining the presence and amounts of the *potent ingredients* may suffice. If the tests have been described in standard journals or other works of reference, these may be cited. The phrase "*physiologically standardized*" or "assayed" is misleading, unless the standard and method are published in sufficient detail to permit of their control by independent investigators.

Rule 3.—ADVERTISING TO THE PUBLIC.—*Preparations and articles promoted to the public for use in the treatment of disease will not be accepted except as specified in the following comments.*

*Lay Advertising.*—Indiscriminate self-medication by the public involves grave dangers, such as misdirected and inadequate treatment, failure to recognize serious disease until it is too late for effective treatment, and the spread of infectious diseases when hidden from a responsible physician. All these are involved in the advertising of drugs to the public, with the further dangers of suggesting by description of symptoms to the minds of the people that they are suffering from diseases described, the dangers of the unconscious and innocent formation of a drug habit and the dangers of starting allergic reactions. ✓

*Drugs Which May Be Promoted to the Public.*—These dangers do not apply in equal degree to all articles, and there are instances in which more good than harm is likely to result from advertisements conveying truthful information to the public, if they do not mislead by undue emphasis or suggestion. The proper promotion of such articles will not preclude their admission to *New and Nonofficial Remedies*; but, in view of the potential dangers to the public, such cases must be carefully weighed and will be confined to the following groups: (a) disinfectants, germicides and antiseptics, provided they are promoted only as prophylactic applications to superficial cuts and abrasions of the skin; (b) laxatives when promoted in such a manner as is not likely to lead to their abuse; (c) antiserums and fractions thereof, vaccines and diagnostic reagents derived from infectious agents; (d) other preparations and articles which in the opinion of the Council could be safely used by the public for the relief of symptoms (such as antacids and analgesics). Each group will have to carry adequate and acceptable labeling statements such as "for the relief of minor aches and pains" for analgesics, and "for the treatment of occasional constipation" for laxatives.

*Unacceptable Advertising to the Public.*—Aside from these specified groups, promotion of articles to the public for the treatment of disease precludes their admission to *New and Nonofficial Remedies*. "Advertising to the public" includes all promotion of the article in newspapers, magazines, radio, films or

any other devices, and placards or circulars which may reach the patient.

This rule imposes no restriction on the legitimate methods of bringing a remedy to the attention of the profession, such as advertising in journals, labeling, circulars and other printed matter distributed solely to physicians, dentists, pharmacists and veterinarians, provided such promotion does not invite or encourage use by unqualified persons.

Advertising the name of a firm as being a reliable one is permissible in any advertising medium.

*Naming Diseases on Label and Labeling.*—The naming of diseases and therapeutic indications in the labeling may be necessary for proper instruction in the use of articles advertised directly to the public and is therefore permissible in the case of the preparations which are accepted for promotion to the public, and where it is required by the Food, Drug, and Cosmetic Act.

*Permanently Affixed Names.*—If a prescribed article is dispensed in its original container, any permanently affixed device that identifies the article to the consumer constitutes advertising to the public. This includes bottles which have the name of the article blown into the glass, and other devices by which the name or initials or other distinctive mark of the article is permanently stamped on the container, on the article itself, or is on the stoppers or seals. Readily removable labels are not objectionable nor permanently affixed labels on parenteral preparations. The permanent affixing of the firm's initials or name to the trade package is acceptable if such initials or name is not suggestive of the article.

*Use of Accepted Articles for Advertising Unaccepted Articles.*—The Council does not countenance the use of an accepted article for advertising other articles which have not been accepted by the Council. The Council therefore objects to the mailing of circulars for accepted and unaccepted articles in one envelope if there is reason to believe that the method of presentation may mislead the reader and if it is not made clear beyond doubt, for instance by the initials N. N. R., which of the products have been accepted by the Council and which have not been accepted. This clause does not apply to advertising material circulated exclusively to dealers.

When, in the opinion of the Council, a firm employs the acceptance of an article in a way that promotes the exploitation of articles that are opposed to the principles of the Council, this may be considered as evidence of bad faith which may cancel the acceptance of all preparations of that firm.

*Acceptance of Article Offered Under Another Name.*—The Council does not accept an article or continue the acceptance of an article if the same article or an essentially similar one is marketed as a therapeutic agent in the United States by the same firm under another name which has not been recognized.

*Advertisements in Foreign Countries.*—The Council may take into consideration any statements made regarding an article or any method of advertising employed by the manufacturer or his authorized agents or representatives, whether in this country or abroad. No objection will be raised to the use of a statement such as "This substance is accepted by the Council on Pharmacy and Chemistry of the American Medical Association under the name of . . ." when such a statement is used in the promotion of a Council accepted preparation sold outside the United States under another name, provided the firm makes no misleading claims and meets the other rules of the Council.

The Council does not regard as within its scope the acceptance of articles marketed solely outside the United States.

*Films.*—The Council holds that the term "advertising" includes "advertising literature," films and similar devices for informing the public or profession.

Rule 4.—THERAPEUTIC CLAIMS.—*When an article is accepted, therapeutic representations by the manufacturers or their agents must be confined to those given in N. N. R. or accepted by the Council between revisions of N. N. R.*

*Unwarranted Therapeutic Claims.*—Manufacturers or their agents are held responsible for all statements made or quoted in any of their advertising concerning the therapeutic properties of their products. These must be compatible with demonstrable facts.

*New Claims.*—Claims that are not in harmony with already accepted facts or supported by acceptable evidence are not admitted. Therapeutic claims made subsequent to the acceptance of an article must be submitted to the Council for review, if such claims exceed, or substantially modify, those made at the time of acceptance.

*Claims for Nontoxicity.*—Claims for nontoxicity are admitted only when they do not conflict with known facts. Physicians are cautioned that a claim of lack of toxicity means only that toxic effects have not as yet been recognized with the doses that have been studied. Apparently justified beliefs concerning this point are often ultimately reversed by extended experience. This applies also to claims that drugs are nonirritating.

*Clinical Evidence.*—To be acceptable, the clinical evidence must offer objective data with such citation of authority as will enable the Council to confirm the facts and establish the scientific value of the conclusions. The amount and character of the evidence which is required depend on the inherent probability of the claims; no evidence is needed for a self-evident claim; very strong evidence is needed when the claim is contrary to the accepted data of science. The acceptability of evidence is determined mainly by its quality. Multiplication of inaccurate observations does not render them accurate. The evidence must be furnished in sufficient detail to permit judgment as to the care with which it was gathered and the legitimacy of the deduc-

tions. Comparative trials facilitate and are often necessary for such judgment. Observations that are not described with sufficient detail to permit verification are subject to suspicion. The credibility of the data and the justification of the deductions are influenced by the reputation and experience of the investigators as to disinterestedness, technical ability and critical judgment. Anonymous communications and observations gathered without adequate facilities are usually worthless as evidence.

*Advertising Copy.*—In commenting on advertising material, the Council endeavors to indicate the type of claims which are acceptable and the nature of objectionable statements. It is not a function of the Council to edit advertising copy word for word, but rather to indicate the general type of revision required. The Council holds the firm responsible for compliance with the specifications of the Council's objections and expects the spirit and intent of such objections to be observed in the remainder of the copy not specifically criticized.

Claims advanced in labeling, proposed advertisements and other promotional material should not exceed those which the Council permitted at the time that it first gave consideration to the drug concerned or those that the Council may have subsequently found acceptable. Such claims may be found in *New and Nonofficial Remedies*.

As new pieces of advertising copy are prepared they should be made available for Council examination or Council files. If the new material is merely reprinted from material previously accepted by the Council, it will not be necessary to have it reviewed by the Council. However, if the material presents new claims, it must be accompanied by supporting evidence for Council consideration. Since the claims of the manufacturer are judged largely by their advertising, noncompliance of the manufacturers with the Council's request for copies of the current advertising may be sufficient ground for the rejection of an article.

*References to Medical Literature.*—References to medical literature in advertising for an accepted product should be accompanied by the name of the investigator and year of publication, or by full reference to the publication to which reference is made.

*Use of Physician's Signature.*—The use of the personal signature of a physician or the facsimile of such signature on the label or in advertising of products tends to create an exaggerated or misleading impression of therapeutic value, through the implication of personal supervision, and articles so labeled or advertised are therefore not acceptable.

**Rule 5.—PROTECTED NAMES.**—*Trademark names for medicinal articles are accepted if the Council deems the use of such protected names not to be harmful to health and if the common or generic names are not unduly subordinated to such trademarks in the labeling and advertising of the products.*

*Advantage of Generic Names.*—The Council believes that medical science is promoted by the use of a single ("generic") name for each drug, based on scientific principles and freely available to all. This would avoid much needless tax on memory with its attendant confusion and errors.

*Rights to Protected Names.*—On the other hand, the Council recognizes that the discoverer of a new remedy has a legal right to a restricted name and that the manufacturer who undertakes the expense of its practical development has a right to some protection and may not feel justified in undertaking the risk if this right is denied.

The Council has therefore conceded acceptance of a protected name to the discoverer or to the firm which first introduced the article. Experience has shown, however, that this restriction to one protected name tends to undue prolongation of the monopoly and that it prevents the control of the Council over competing brands which could be made acceptable except that they employ competing protected names. The Council therefore deems it advisable to accept several protected names for the same article, provided there are no reasons which would render this especially objectionable and harmful, and provided the common or generic name is not unduly subordinated to the protected name, in the opinion of the Council. This means that accepted drugs should always be identified by adding the generic or official name when the protected name is used, as, for example, "Luminal, brand of phenobarbital," and "Benzedrine, brand of amphetamine."

Physicians can protect themselves against much confusion by using the official names in speaking or writing of these drugs.

*Objectionable Names.*—Names which are misleading or which suggest diseases, pathologic conditions or therapeutic indications are not acceptable (the provision against therapeutically suggestive names does not apply to serums, vaccines and antitoxins).

In the case of pharmaceutic preparations or mixtures the name must be so framed as to indicate clearly the most potent ingredients.

Coined names for salts will not be accepted unless such names indicate the components of the salt; coined names for new substances marketed as pharmaceutic preparations will not be accepted unless such names indicate definitely the type or dosage form of the article.

*Protected Names for Unoriginal Articles.*—Protected names will not be recognized for articles which are included in the U. S. Pharmacopeia or National Formulary, or while they are tentatively adopted for such inclusion, unless the name was in public use before the drug was admitted to or tentatively adopted for these books. The date of tentative adoption is understood to be that of the first galley proof of the U. S. P. or the N. F. containing the article concerned.

Protected or coined names that are applied to either official or nonofficial dosage forms (or simple modifications thereof) of official substances are likewise not acceptable.

In the marketing of unoriginal articles, the legitimate interests of the producer are sufficiently served by identifying such products by appending the name of the manufacturer or agent or by the use of a general brand mark. No objection is made by the Council to the use of such brand marks, provided that such mark is not used as a designation for an individual article. Names, initials or brand marks of manufacturers or agents when used to denote proprietorship shall not be of such character as to cause any misunderstanding or confusion as to their significance.

*Pharmaceutic Preparations and Mixtures.*—A protected name may be accepted for a pharmaceutic mixture on the ground of originality and if it is a distinct improvement over available preparations. This is exceptional, for pharmaceutic preparations rarely involve sufficient originality and it is important that their names should remind the prescriber of their potent ingredients. The Council recognizes, however, that the development of the practice of pharmacy has been along lines which make it undesirable at times to prepare complicated ointments and suppositories extemporaneously and that there is a tendency for such preparations to be manufactured ready-made by the manufacturers for prescription by physicians.

The Council may also recognize coined names for pharmaceutic preparations or mixtures that were in actual use before the establishment of the Council and that have been used continuously since that time, and names for mixtures that were named under the reasonably justified bona fide belief that they were chemical compounds, provided such coined names are not otherwise objectionable.

*Coining of Name.*—The Council recommends that trade names be coined so as to indicate the potent element or constituent.

*Naming Salts.*—Difficulty frequently arises from the application of coined names to salts. For example, a firm introduces the hydrochloride of a synthetic base under the name "Artificialine." Subsequently the firm decides to introduce the lactate of the same base. If this is called "Artificialine lactate" the name "Artificialine" will now mean the base instead of the hydrochloride which is being marketed under that name. In order to avoid this confusion the Council holds that coined names for salts will not be accepted unless such names indicate the components of such salts, thus "Artificialine hydrochloride"; the name "Artificialine," unqualified, is acceptable only for the base.

A similar difficulty may arise when a product is marketed first only as a pharmaceutic preparation to which the manufacturer wishes to apply a short coined name, for example, an elixir of a new hypnotic under the name "Aliphal." If later the manufacturer elects to market the substance also in powder form, an entirely new name would become necessary and this would

cause confusion both to the profession and to the trade. The Council therefore holds that coined names for new substances marketed as pharmaceutical preparations will be accepted only if such names indicate the type or dosage form of the preparation, thus "Elixir of Aliphal," "Aliphal Powder," not "Aliphal" unqualified.

For declaration of benzyl alcohol or chlorobutanol in the name of a product, see comments under Rule 1.

*Biologic Products.*—A biologic product intended for use as a diagnostic reagent, vaccine or antibacterial or antitoxic serum should be designated by a name which indicates its biologic nature, e. g. tuberculin, rabies vaccine, diphtheria toxoid, diphtheria antitoxin. A protected name will be recognized for inclusion in N. N. R. only if it clearly indicates the nature of the product.

*Use of Numerals and Letters.*—Since the use of numeral or alphabetical designations in connection with drug names tends to take the emphasis away from the name and to displace the name, thus leading to confusion, the Council will not recognize the name of a drug in which the numeral or letter is an integral part of the name, except in special cases in which the use of a numeral or letter seems desirable because further improvement of the product is anticipated, in which case the Council may grant a special exemption from the rule. Under this rule the use of numerals or letters in connection with the name of a product will not be permitted on labels or in advertising unless the numeral or letter is clearly separated from and subordinated to the name by type and if feasible by position. This rule does not apply to price lists and catalogues.

*Rule 6.—PATENTS AND TRADEMARKS.*—*If a preparation or product is patented as to process or product or both, the number of such patent or patents must be furnished to the Council. If the name of an article is registered or the label copyrighted, the registration (trademark) name and number and copies of the protected label must be furnished to the Council.*

This information is essential to determining the legal status of the article. If it is registered in a foreign country under a different name, this information should also be supplied so as to identify the article in the foreign literature.

*Rule 7.—UNSCIENTIFIC AND USELESS ARTICLES.*—*A preparation or an article will not be accepted if in the opinion of the Council it will not be in the best interests of rational medicine and the public.*

Useless drugging is apt to be harmful. This precludes the acceptance of articles which have no definite therapeutic value, of compounds or mixtures with an excessive number of active ingredients or with ingredients that are of no probable assistance to each other, and of articles which involve dangers of toxic effects disproportionate to their therapeutic value.

## GENERAL EXPLANATORY COMMENTS

*Substances Described in New and Nonofficial Remedies.*—In the book are described pharmaceutic and drug substances if they have originality or other important qualities which, in the judgment of the Council, entitle them to such place; official preparations concerning which the Council deems the medical profession not yet fully informed; or any other article the inclusion of which is believed to give useful information to the physician.

*Previous Noncompliance.*—The Council judges an article by the facts in evidence at the time of its presentation. Previous non-compliance with the rules (short of intentional fraud) does not prevent at a later date the favorable consideration of an article which is in accord with existing rules.

*Reconsideration.*—Infringements of the rules after acceptance of an article for *New and Nonofficial Remedies*, or the discovery that the Council's information was incorrect, will cause the acceptance to be reconsidered and may be followed by the omission of the article and publication of the reasons for such omission.

*Acceptance Not an Indorsement.*—The admission of an article does not imply a recommendation for its use. Acceptance simply means that the Council has found no conflict with its rules.

It may not be superfluous to point out that it is not a function of the Council to determine whether a product complies with the federal, state or municipal laws and regulations. The responsibility for this lies with the manufacturer himself.

*Seal of Acceptance.*—For articles which are accepted for inclusion in *New and Nonofficial Remedies* the Council permits the use of its official seal of acceptance on the packages of the article and in the advertising for it with the following stipulations: 1. If the seal is used in price lists and catalogues which also feature unaccepted articles, it must be used for accepted articles in such manner that there can be no implication that the seal applies to the unaccepted articles. 2. The following statement in reference to the significance of the seal may be used in connection with the seal: "The 'accepted' seal denotes that [name of article] has been accepted for *New and Nonofficial Remedies* by the Council on Pharmacy and Chemistry of the American Medical Association." Further statements in regard to the seal must be submitted to the Council and be found acceptable before they may be used. 3. The size of the seal on the package shall not be greater than one inch in height or diameter, and in advertising it shall be in proportion to the dimensions of the advertisement so as to afford ready recognition; but undue size, giving greater prominence to the seal than to other important features of the advertisement or detracting from the dignity of the seal in the opinion of the Council, will not be permitted. 4. When for any reason the acceptance of an article is rescinded, the seal must not appear on new labels or in new advertising for such article; and old labels and advertising which



feature the seal must not be in circulation, in evidence or before the public longer than six months subsequent to notification of the revocation.

*Duration of Acceptance.*—Unless otherwise determined at the time of acceptance, articles admitted to *New and Nonofficial Remedies* will be retained for a period of three years, provided that during that period they comply with the rules and regulations which were in force at the time of their acceptance. Evidence indicating that the compliance with the rules no longer exists, for instance, with regard to unwarranted therapeutic claims, will be considered the basis for reconsidering the acceptance before the end of a period of three years.

At the end of this period, all articles will be re-examined for compliance with existing rules. Particular weight will be given to the question whether claims for the therapeutic value of the preparation are sustained by recent statements in the literature and by the general esteem in which the preparation is held by clinical consultants of the Council. The reacceptance of articles after such re-examination shall be for three years unless a shorter period is specified.

Amendments to the rules, by specific requirements or by interpretation, which may be made after the acceptance of an article shall not apply to such article until the period of acceptance has elapsed. At the end of this period the article, if it is not eligible under the amended rules, will be omitted.

*U. S. P. and N. F. Articles.*—A product which has been official for more than 20 years will not ordinarily be considered for inclusion or retention in *New and Nonofficial Remedies*; but all preparations which are licensable under the Serums, Virus and Vaccine Act, including arsenicals for the treatment of syphilis, are eligible for consideration for inclusion or retention in *New and Nonofficial Remedies*, regardless of their official status.

*Mixtures.*—The Council will accept for inclusion in N. N. R. only those mixtures that present some real advantage. The Council endorses the principle that prescriptions should be written on the basis of the therapeutic effects of the individual ingredients. It recognizes, however, that at times it may be advantageous to prescribe more than one ingredient in the same product. A further explanation may be found under explanatory comments on Rule 5.

*Diagnostic Reagents.*—Reagents and other drug preparations which are not used in or on the human body are not considered for inclusion in N. N. R. At the request of the distributor the Council may determine the status of such products individually.

## PRESENTATION OF ARTICLES FOR N. N. R.

### ELIGIBILITY FOR N. N. R.

Before submitting any article for inclusion in N. N. R., a careful study of the Official Rules and of N. N. R. should be made to determine its eligibility for acceptance by the Council.

Articles of questionable eligibility may have their status determined prior to formal presentation on request of the manufacturer. Such preliminary requests directed to the Council office may avoid waste of time for all concerned.

New drugs, not yet released for commercial distribution by the Food & Drug Administration, will not be accepted until passed by that agency unless it seems evident that the product will be placed in interstate commerce. The Council restricts acceptance to articles that are available on the market or soon to be placed thereon and to articles that are marketed in the United States.

1. Articles belonging to a class of preparations already rejected by the Council and for which new evidence is lacking to overcome previous objections are obviously ineligible for inclusion in N. N. R. A cumulative list of references to reports of the Council on articles previously rejected or on which unfavorable action has been taken will be found in the Bibliographic Index of N. N. R.

2. Articles that have had official (U. S. P. or N. F.) status for more than 20 years (except products licensable under the Serums, Virus and Vaccine Act, including arsenicals for syphilis, which are admissible) or have been specifically exempted from consideration by previous action of the Council, are likewise in general ineligible for N. N. R. (Report of the Council: Preparations Exempt from Council Consideration, J. A. M. A. 129: 1017 [Dec. 8] 1945).

3. Articles advertised to the public without adequate directions for use or against abuse or that are not considered safe for use by the general population without medical supervision are ineligible for inclusion in N. N. R. Thus far the Council has classified as safe for public use (a) antiseptics for prophylactic application to minor injuries of the skin, (b) laxatives not prone to abuse, (c) antacids and analgesics that can be safely used for the temporary relief of symptoms, (d) pediculicides which are considered safe for self-application.

4. Articles of nonmedical significance or that are not intended for the diagnosis, prevention or treatment of disease are not eligible for N. N. R. Thus, articles not used in or on the human body, or used outside the body for purposes that are not directly or indirectly of medical significance, would not come within the purview of the Council.

5. Instruments or devices per se that do not directly involve consideration of some medicinal or pharmaceutical substance are also outside the purview of the Council.

*Method of Presentation.*—The procedure in submitting an article to the Council consists in forwarding to the Secretary: A complete description of the product (dated and signed) *in duplicate*, in accordance with the form outlined in subsequent paragraphs; three trade packages of each dosage form of the product to be considered (not to include more than one quantity

package of identical lots of the same item); one sample of *each active ingredient* contained in the product; 22 copies each of all labels (container, package, carton), package enclosures (leaflet or circular) for each submitted dosage form and of *each piece of advertising* for the product that is distributed or intended for distribution. In the event no promotional material other than labeling is employed, a statement to that effect should be made, with the understanding and agreement that should advertising or promotional material subsequently be proposed for distribution, copies of such material will be submitted to the Council *before it is placed in distribution*. Advertising for submitted articles that mentions other products not submitted or not already accepted by the Council for inclusion in N. N. R. cannot be approved for distribution unless the advertising is revised to eliminate the unaccepted items.

Consideration is expedited if the labels are mounted on normal size letter paper so that 22 separate sets of labels will be available for examination. In the case of new drugs or of well known articles for which new therapeutic claims are advanced, the outlined description should be supplemented by 22 copies of reprints (or suitable abstracts) of all available experimental and clinical evidence including references to the published scientific literature or other sources from which it is derived. The Council considers it the responsibility of the manufacturer to furnish evidence to support all claims made for products that it markets. When the article submitted represents only a new brand of a preparation already described in N. N. R., such evidence is not required so long as the claims do not go beyond the statements made in that publication. When the article is simply a dosage form of a brand of the product already accepted, only that information essential to supplement the original presentation of the article to afford a clear description of the composition and purpose of the new dosage form is required, in addition to the necessary specimens and copies of the labeling and any new advertising. When two or more dosage forms of the same product are submitted together, the information may frequently be combined in the same outline when that is feasible. The inclusion of unacceptable dosage forms (or mention of them in the advertising) in a presentation submitted for otherwise acceptable items of the same product frequently causes delay in acceptance of the recognized dosage forms. Separate outlines for dosage forms involving special vehicles or bases may avoid the confusion that sometimes arises in this connection. The Council has restricted acceptance of certain products to dosage forms of specific size or concentration that is indicated either in the Official Rules or in N. N. R. under the general statements for the class of articles affected.

#### OUTLINE OF DESCRIPTION

1. *Name of Product*.—The protected (trademark) or coined name, if any, should be supplied; otherwise the common name used to designate the product may be given. The common name should, when applicable, conform to the official (U. S. P. or

N. F.) designation or the nonproprietary (generic) name adopted by the Council. Protected names should comply with all stipulations of rule 5 concerning acceptable nomenclature and should be followed at this point of the outline with a brief explanatory statement of the significance and reason for choice, together with the date the name was first used publicly to designate the product. (The Council does not recognize protected names that were not in public use prior to admission of the article to official status in the U. S. P. or N. F. or tentative adoption for inclusion in these books.) The name (protected or otherwise) should be reasonably descriptive if possible of the principal active ingredient, should include the designation of the salt when it is present in such form, and, when applied to specific dosage forms, should include an appropriate designation of the nature of the product and the quantity or concentration of the active ingredient, e. g. Tablets Phenobarbital, 0.1 Gm., Solution Phenobarbital Sodium 10 per cent. Likewise, certain ingredients that may be present in sufficient amounts or concentration to produce a prominent, though secondary, therapeutic effect (intended or otherwise) are required to be declared as part of the name for the product, e. g. Solution Sodium Morrhuate 5 per cent with Benzyl Alcohol 1 per cent. Care should be taken that the name given and its word order corresponds to that shown on the submitted labeling and advertising.

2. *Synonyms*.—The official or N. N. R. name that may be used for prescribing when a protected or coined name is used to designate the product should be submitted; if marketed only under an official, Council-adopted or common or generic name, any other appropriate synonym that may be applicable is satisfactory. When a protected name is used, and an official or Council-adopted nonproprietary name does not exist, one or more suggested nonprotected names suitable as a generic designation should be submitted for consideration by the Council's Committee on Nomenclature. In all cases when a protected name is used, the official or N. N. R. name is required to be displayed on the labeling and advertising, with sufficient prominence to permit ready identification of the product, e. g. Tablets Luminal (Brand of Phenobarbital), 0.1 Gm.; Solution Luminal Sodium (Brand of Phenobarbital Sodium), 10 per cent.

3. *Definition*.—If the article represents a definite substance, its scientific name and its structural chemical formula so far as this can be ascertained must be submitted. If the article is a mixture or is submitted in the form of tablets, solution, ointment or the like, a quantitative statement of composition of all active medicinal ingredients, including preservatives, vehicle, base or excipient, preferably in percentage form (when applicable) and in the metric system should also be offered. Unless otherwise indicated, per cent figures will be understood to follow the meaning of percentage as defined for the U. S. P. Labeling should carry a quantitative declaration of all active ingredients unless this is clear from the name used to designate the product and, in the case of injectable preparations, must include a declaration

of the presence of any preservatives that are added. The identity of the vehicle or base in the case of solutions, suspensions or ointments not self evident from the name should be specifically stated on the label. In the case of biologic products for injection or topical application to denuded surfaces, the Council encourages the declaration of the animal source of the material because they are capable of precipitating allergic reactions in sensitive persons.

4. *Preparation.*—The description should contain a general statement of the process of manufacture. Details of the process may be omitted, but sufficient description is to be included to enable the Council to assure itself that the process will result in a product of the claimed identity, strength, quality and purity. Particular attention should be paid at this point to indicate all control procedures used to detect errors in manufacture and to insure the satisfactory character of the finished product. The Council requires detailed information concerning the methods used to control the potency and composition of each dosage form that is submitted.

Manufacturers must submit a statement concerning the control processes used for each product submitted to the Council, except insulin, penicillin, streptomycin or other preparations that are certified by the Food & Drug Administration. Unnecessary duplication of such information for other products may be avoided by supplying a general statement as outlined below, to apply to all articles of a given class, or when feasible, to all products marketed by the firm; provided that reference is made to such previously furnished general statement(s), together with such additional information as may be needed to explain any pertinent variations applicable to the product under consideration or any subsequent changes in the control procedure that may be adopted.

✓ The description of control procedures should include information on each of the following points (where applicable):

- (a) Precautions to insure proper identity, strength and purity of the raw materials.
- (b) Precautions to preserve sanitary conditions in space allotted to storage of raw materials.
- (c) Whether or not each lot of raw materials is given a serial number to identify it and the use made of such numbers in subsequent plant operations.
- (d) Method of preparation of formula card and manner in which it is used. Specimen blanks of the forms used should be supplied in duplicate.
- (e) Manner in which weights and measures of each individual ingredient are checked when preparing formula.
- (f) Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and at what stage and by whom this is done.
- (g) Methods of maintaining sanitary conditions within the manufacturing plant and avoiding contamination of the drug with filth, dust and extraneous material.

- (h) Precautions to check the total number of finished packages produced from a batch of the drug with the theoretical yield.
- (i) Precautions to insure that the proper labels are placed on the drug for a particular lot.
- (j) The analytical controls used during the various stages of the manufacturing, processing and packaging of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are submitted. If the article is one which is represented as sterile, the same information should be given for sterility controls.
- (k) An explanation of the exact significance of any control numbers used in the manufacturing, processing and packaging of the drug, including any code numbers which may appear on the label of the finished article.
- (l) Additional procedures employed which are designed to prevent contamination and otherwise insure proper control of the product.
- (m) Are representative samples of each lot of the drug examined by any other laboratory (government or private) prior to distribution? If so, by whom?

5. *Properties*.—Appearance, odor, taste and any characteristic physical-chemical properties such as melting point, boiling point, solubility and any important incompatibilities must be stated.

6. *Tests*.—If the article is a chemical substance, there must be submitted adequate tests of identity, strength, quality and purity, including methods of assay. Upper and lower limits of acceptability for ingredients assayed are to be indicated. If the product is a mixture, methods for identification and assay of principal active ingredients are necessary. For vitamin preparations or other substances which must be biologically assayed, protocols of several typical assays, signed by a reputable biological chemist or other qualified assayer, should be presented. If the article is one which is represented to be sterile or because of its manner of use should be sterile, the methods used to determine its sterility, including method of sampling, bacteriologic method, frequency of examination and other pertinent information should be given. All methods should be described in accordance with the style of N. N. R. or of the U. S. P.

7. *Pharmacologic Action*.—General information is necessary concerning the absorption, actions, toxicity and fate or excretion of the preparation, particularly as applied to the manner in which it is intended to be used, i. e. by injection, oral administration or topical application. In the case of disinfectants, anti-fungal agents or spermicides the appropriate experimental tests made to demonstrate the efficiency of the product should be outlined in accordance with the Council's criteria. When such data are required for specified classes of articles or when the product is a new drug, these detailed reports should be separately compiled (in abstract form if extensive) and 22 copies supplied as a supplement to the information given under this heading.

8. *Therapeutic Indications.*—A brief statement of the conditions and/or diseases in which the article is claimed to be indicated is necessary. This should include any diagnostic and prophylactic as well as therapeutic uses. These should correspond to the actions and uses given in N. N. R. when applicable. If additional claims are advanced, all claims must be supported by the pharmacologic or bacteriologic evidence given in the preceding section and by clinical studies to be outlined under this heading. In general, this should include a summary of the various conditions treated, the number and type of cases treated, the dosage, frequency and duration of the administration of the drug, the therapeutic effects and any untoward reaction observed. The actual clinical data, including a bibliography, should be furnished as a separate supplement to this part of the presentation, accompanied with 22 copies of each protocol, reprint or other suitable reproduction of the evidence. When extensive, the detailed reports may be submitted in duplicate and 22 copies of a suitable comprehensive and unbiased summary or abstract furnished for the Council. Care should be taken to see that the therapeutic claims that appear in the advertising for the product correspond to the indications and evidence given in this presentation.

9. *Dosage.*—When applicable, the dosage and method of administration recommended should correspond to the one specified in N. N. R. When the product is a new dosage form of an article otherwise described in N. N. R., the details of dosage and administration for the proposed product should be given, together with any necessary precautions peculiar to its mode of application. Similar care should be taken to supply all essential dosage information for a new drug.

10. *How Supplied.*—A list should be given of all dosage forms, sizes and package forms of the article that are intended for consideration by the Council and that are described in the foregoing outline. A statement should also be included to indicate whether or not the active ingredient is marketed in bulk.

11. *Manufacturer.*—The name of the firm that is responsible for the finished article as labeled and the names of the manufacturers of all ingredients contained in the article must be stated.

12. *Patents and Trademarks.*—When pertinent, the number of the U. S. patent and number of the patent in the country of origin is necessary. If the article bears a registered trademark, its number and, if registered in foreign countries, the name or names under which it is so registered is also required.

If the product is one of which no brand has been previously admitted to *New and Nonofficial Remedies*, the manufacturer or responsible agent must present protocols of laboratory and clinical evaluations (toxicity, pharmacology, therapeutics, deterioration, etc.). Such protocols should include not only evidence collected by the firm in its own investigations, but references to published papers if available. Twenty-two copies of this material

must be provided so that each member of the Council can examine at first hand all submitted evidence. If the material is so exhaustive that 22 copies are impracticable, the firm may submit only two copies of all evidence and 20 copies of an unbiased abstract of the evidence. The abstract, in fact the entire presentation, may be submitted in mimeographed form.

Firms submitting for the first time an article eligible for inclusion in N. N. R. are required to supply the following additional information (*in duplicate* unless otherwise indicated) at the time the first such presentation is made to the Council:

(a) Price list or other suitable tabulation of all products sold by the firm for human medicinal use; 22 copies of catalogue and/or price list to be submitted.

(b) A statement of the laboratory and control personnel of the firm and their qualifications.

(c) A general statement of the firm's policies with respect to its scientific aims and methods of marketing drugs either for the public or for the profession. This should include present practices as well as any future plans.

(d) A statement, signed by a responsible officer of the firm, that it agrees to notify the Council promptly on the discovery that an error has been found in the compounding of any of its Council-accepted preparations, either by the firm itself or by a government or other outside agency, that causes the article to differ from its standard of identity, strength, quality or purity.

(e) A statement, also properly authorized, that the firm agrees to abide by the rules of the Council as applied to brands of its articles that may be accepted for inclusion in N. N. R. and to submit to the Council before implemented all future proposals for changes in the composition, labeling, advertising or market status of such products.

## CRITERIA FOR THE EVALUATION OF CERTAIN PRODUCTS

Certain groups of products present problems that can best be solved when uniform consistency is maintained in the collection of evidence for the preparations in these groups. Accordingly, the Council from time to time proposes criteria to serve as guides in the planning of experiments and the examination of results intended to obtain data to meet the Council rules. So far the Council has prepared criteria for anti-infective agents, anti-fungal agents and contraceptive agents.

**ANTI-INFECTIVES.**—For new products (i. e. not in N. N. R.) involving claims of antiseptic, bacteriostatic, or germicidal effectiveness, or when new claims are advanced, protocols of bacteriologic examination signed by a reputable bacteriologist, and evidence of clinical usefulness which will present studies on toxicity, pharmacology, etc., should be submitted. Where published papers are available, references should be cited.



Criteria for evaluation of skin disinfectants which the Council deems advisable include:

(A) For Antibacterial Agents—

1. Phenol coefficients or other in vitro tests in the absence and in the presence of serum, using both vegetative bacterial cells and clostridial spores, with suitable recovery mediums containing, if known, neutralizing substances for the disinfectant being tested.

2. Data on germicidal efficiency under conditions simulating actual use by the method of Price (Price, P. B.: the Bacteriology of Normal Skin: A New Quantitative Test Applied to a Study of the Bacterial Flora and the Disinfectant Action of Mechanical Cleaning, *J. Infect. Dis.* 63:301 [Nov., Dec.] 1938; Ethyl Alcohol as a Germicide, *Arch. Surg.* 38:528 [March] 1939) or, better still, by an extension of the method of Price (Bernstein, L. H. T.: Standardization of Skin Disinfectants, *J. Bacteriol.* 43:50 [Jan.] 1942). The complications due to possible effects of the germicide on the skin itself should be taken into consideration (Cromwell, H. W., and Leffler, Ruth: Evaluation of "Skin Degerming" Agents by a Modification of the Price Method, *ibid.*, p. 51).

3. Data on germicidal efficiency by an animal method, such for example as suggested by Alice H. Kempf and W. J. Nungester (An In Vivo Test for the Evaluation of Skin Disinfectants, *ibid.*, p. 49) or R. W. Sarber (*ibid.*, p. 50).

4. Evidence from animal experiments regarding irritant action on skin and mucosae and regarding systemic toxicity.

5. Critical clinical evidence supporting claims of harmlessness and efficacy.

6. Data on the bacteriostatic activity as distinguished from the germicidal activity of the disinfectant.

(B) For Antifungal Agents.—An extensive discussion of this subject appears in *The Journal* as a Council report (July 14, 1945, vol. 128, pp. 805-811). For guidance the data suggested may be divided into three parts: (1) laboratory tests of the fungicide, (2) clinical tests and (3) toxicity tests, and obtained as follows:

1. *In Vitro Tests of Fungicide.*—The phenol coefficient test for disinfectants and antiseptics as modified by the American Public Health Association subcommittee should be used. For convenience, this is resubmitted, but in synoptic form. A detailed report is published in the *American Journal of Public Health* for 1945 of the Standard Methods Committee for the Examination of Germicides and Antibacterial Agents.

- (a) The test fungus should be *Trichophyton interdigitale*. A suitable strain, No. 9533, is procurable from the American Type Culture Collection, Georgetown University, 3900 Reservoir Road, Washington, D. C. It should survive ten minutes' exposure at 20° C. to phenol 1:60 but not to a strength of 1:45.

(b) Spore suspensions of this test fungus should be prepared from ten day agar cultures in a concentration of 5 million conidia per cubic centimeter. For performing the test, 0.5 cc. of this suspension is added to 5 cc. of the fungicide concentration being tested.

(c) Samples for viability tests should be taken at five, ten and fifteen minute intervals and planted in a liquid medium containing 1 per cent Difco Neopeptone and 2 per cent chemically pure dextrose, pH 5.6-5.8. A liquid medium is essential for the rapid dissipation of the fungicide carried over. In the case of fungicides exerting a strong fungistatic effect, subcultures must be made.

(d) The so-called "*Trichophyton rosaceum*" should not be used as a test species. It is less resistant than *Trichophyton* when tested by the method outlined here, although it often appears to be more resistant in plate tests.

The test procedures follow the plan outlined in United States Department of Agriculture Circular 198 for the determination of phenol coefficients.

**2. Clinical Tests and Their Evaluation.**—This involves the use of prepared preliminary outlines and of a protocol for each patient.

(a) Selection and Grading of Patients: The number of patients should be sufficiently large to permit their division into a test group and a control group. Each of these, in turn, should be large enough to permit results that will be significant when later divided into subgroups for purposes of analysis. In consultation, a group of dermatologists has estimated 50 as the minimum number for both the test and the control group. Bed patients are not suitable, because dermatophytosis sometimes disappears spontaneously with bed rest.

Each of the two groups should contain an equitable representation of mild, moderate and severe cases. It is advantageous to indicate on a diagram on the protocol just what the extent and type of lesion are for each patient.

(b) The Environment: This and other circumstances should be comparable in the two groups. The groups should be tested simultaneously. Thus, results from group A which were secured in winter would not be comparable to ones secured on group B in the summer; dermatophytosis is worse in the summer. Similarly, results should be checked with age groupings in the two test groups lest it have too much of a disturbing influence in the evaluations. Youths are far more predisposed than the aged.

(c) Laboratory Diagnosis: As a check against the clinical diagnosis, scrapings should be examined under the microscope for the presence of fungus and also cultured at the beginning of the studies. These examinations should be regarded as only supplementary to the clinical findings; many cases of valid dermatophytosis fail to yield confirmatory laboratory evidence, but the laboratory examinations may clarify doubtful clinical cases,

and a knowledge of the identity of the species may be valuable when analyzing therapeutic results later. Thus, a fungicide might be eventually discovered which was efficacious against *Trichophyton purpureum* or other fungus but not against other species, and vice versa.

(d) Number and Duration of Treatments: As a working rule, applications should be made night and morning for two weeks. A final or subfinal examination should be made at the end of four weeks.

(e) Faithfulness of Patient to Treatment: The investigator should appraise the human type of each patient before admitting him to the test series and have no hesitance in rejecting the unpromising ones. Lapses in treatment demand that the patient be removed from the series and is one more reason for securing a larger number of patients at the beginning of the work than will be employed in the final evaluation.

(f) Privacy on Part of Patients: Patients should be requested not to discuss their treatment programs with other patients; they may influence one another's opinions. For obvious reasons, clinical tests should not be conducted on patients who are employed in plants which have a gainful interest in the fungicide being tested.

(g) Local Irritant Effect of Fungicide: This should be substantially nil, considering the number of fairly effective therapeutic agents now existent which are free from irritant effects. Certainly, the development of any reactions that are at all severe should at once condemn the agent.

(h) Sensitization to the Fungicide: This factor enters into and is routinely inquired for in tests of local applications in general. In the case of dermatophytosis it will largely take care of itself during the clinical tests of fungicidal value, where the applications are "interrupted" in the natural course of events. The appearance of flare-ups shortly after the eighth day of treatment should be watched for. If they do appear, a special set of tests for sensitization must be made.

(i) Toxic Systemic Effects: These should not play a role of importance in the treatment of dermatophytosis. Animal tests should be required save in exceptional circumstances, indicating whether the substance is toxic when administered internally and, if so, the amount that can be absorbed from skin. Such animal tests can follow the plans already developed for bacterial disinfectants and antiseptics. The Bureau of Ships Circular 51D6 (Int.), Dec. 15, 1942, page 4, paragraph F.-2d may be followed in this connection.

(j) Readings of Results of Treatment: These should be made without any knowledge of the identity of the patient or of the treatment that has been employed; an assistant should have removed, if possible, any traces of telltale fungicide that may remain. Only in this way can the factor of bias be completely removed and a fair, impartial evaluation secured. If at all possible, the readings should be made by a disinterested person.

(k) *Mycologic Checks on Therapeutic Results:* These will have value only of a kind supplementary to the clinical opinions because of the increased difficulty in laboratory demonstration of fungi in treated lesions. At the conclusion of therapy they should be made on the "cured" and "nearly cured" patients and again on the cured patients four weeks after cure. Positive results will have larger definitive value because they will indicate that the fungicide has not killed. With negative results there is a possibility that fungi are still present but not demonstrable. In any event this mycologic check should be performed so that the data may be available when making final evaluation. The competence of the examiner in recognition of fungi is of paramount importance.

(l) *Grading of Results:* "Cured," "almost cured," "improved," "stationary" and "worse" are suggested, but each worker is at liberty to select any system that suits his purposes; but he should be clear beforehand for his own guidance as to the criteria for grading; from this there should be no deviation later. A subdivision like this into five grades reduces the number of cases available for subsequent statistical purposes and illustrates once again the necessity for numerous patients to begin with. Opinions of patients as to results should not be depended on too much; in cases of doubt they should be discounted. Patients commonly regard themselves as cured when itching ceases. It will be conducive to accuracy if the physician has an assistant who will independently grade the results, the final grading being decided in consultation on the spot.

3. *Toxicity Tests.*—These should be performed depending on the individual circumstances surrounding the chemical concerned. Where there is a hazard the Bureau of Ships circular entitled "Disinfectant, Germicide and Fungicide," page 4, paragraph F.-2d may be followed. Ten healthy adult albino rats weighing between 150 and 250 Gm. should be employed, none pregnant. They should be fed as usual. Three-tenths cc. of the fungicide (standard strength) per kilogram of body weight should be slowly inserted obliquely into the peritoneal cavity. The animal should then be given the usual food and water and observed for untoward effects for 72 hours.

**CHEMICAL CONTRACEPTIVE AGENTS.**—For guidance in reviewing contraceptive products, the Council on Pharmacy and Chemistry has proposed the following criteria:

1. The use of the word "contraceptive" need not be limited to materials which will prevent conception on every occasion of use.
2. Evidence shall be furnished that use of the material decreases the incidence of pregnancy. This evidence may be secured in connection with occlusive devices unless the manufacturer's advertising is directed chiefly toward the use of the jelly or cream without such devices. It is desirable that each case reported should be observed for at least 12 months, and that the minimum of 75 patient-years of experience should be reported.

(Thus 50 patients for 18 months or 25 patients each followed for 3 years would be the equivalent of 75 patients for 12 months.) If cases are excluded from the series on the basis of their being irregular users, the number excluded and the nature of the evidence justifying their exclusion should be stated.

3. Evidence shall be submitted that 100 or more couples have used the material on six or more occasions without irritation or injury.

4. Evidence is desirable that 12 or more women have received vaginal applications of the recommended dosage on 21 successive days without subjective irritation or injury and without evidence of physical damage shown on speculum examination by a physician with special experience in this field. Thus, inspection of the vagina at least once a week should be done as a protection to the patient in case the jelly proves to be irritating.

5. The quantitative formula from which the contraceptive mixture is prepared shall seem to the Advisory Committee to be safe and, presumably, effective.

6. The consistency shall be satisfactory to the committee. It shall not show separation into more liquid and more solid portions visible to the naked eye.

7. Evidence shall be submitted that the consistency is not substantially changed after storage for 12 months at 27° C.

8. The consistency shall be reasonably uniform from batch to batch.

9. The spermicidal time of the contraceptive material as measured by the method of Brown and Gamble (*Human Fertil.* 5:97 [Aug.] 1940) with proportions of material, isotonic solution of sodium chloride and semen of 1:4:5 shall be 30 minutes or less as measured by the average of four or more tests.

10. The use of jellies or creams suggested by the manufacturer need not be limited to use in conjunction with an occlusive device.

11. If a syringe applicator or nozzle is furnished for use in connection with the jelly or cream, it shall be sufficiently translucent to permit the detection of air which might lead to inadequate dosage.

12. If a perfume is used, a quantitative statement of ingredients is required.

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## DECISIONS OF GENERAL INTEREST

In order to aid manufacturers and distributors of medicinal articles which conform to the requirements of the Council's rules, certain statements which have been adopted by the Council are herewith presented.

### **The Use of Numbers and Letters in Names**

Some time ago the Council adopted the following statement expressing its attitude and requirements with regard to the use of numeral and alphabetical designations in the names of pharmaceutical products :

"Since the use of numeral or alphabetical designations in connection with drug names tends to take the emphasis away from the name and to displace the name, thus leading to confusion, the Council will not recognize the name of a drug in which the numeral or letter is an integral part of the name, except in special cases where the use of a numeral or letter seems desirable because further improvement of the product is anticipated, in which case the Council may grant a special exemption from the rule. Under this rule the use of numerals or letters in connection with the name of a product will not be permitted on labels or in advertising, unless the numeral or letter is clearly separated from and subordinated to the name by type and if feasible by position. This rule does not apply to price lists and catalogs."

The rule has been interpreted to apply also to alphabetical and numeral combinations which are sometimes used as trademarks. Such devices, when used as an integral part of a name or in a manner which would tend to promote their use as a substitute for a proper name, are held to be objectionable.

The guiding principle in the enforcement of this rule is fairly simple. The Council wishes to avoid any disposition of numbers that would tend to make them a part of the name or a substitute for it, in the minds of the prescriber or the public. It countenances their use only for the convenience of the wholesaler.

To aid manufacturers and distributors in the preparation of labels which meet the requirements of this rule, the Council offers the following examples of acceptable and unacceptable number set-ups on labels:

**Acceptable**

ELIXIR BROMIDES COMPOUND No. 42
---------------------------------------

100 cc.	List No. 88
SYRUP EPHEDRINE COMPOUND	

**Unacceptable**

ELIXIR No. 42 BROMIDES COMPOUND
------------------------------------

SYRUP EPHEDRINE COMPOUND No. 88
---------------------------------------

(The typography of the numbers in the "acceptable" labels should be subordinate to that of the name itself.)

These examples do not cover all types of labels but they should serve to give some idea of what the Council is attempting to accomplish in the way of compliance with its rule prohibiting the use of numbers as integral parts of names.

These principles apply also to collateral advertising. No objection will be made, however, to a statement in the concluding paragraph of the text of an advertisement or circular to the effect that the product advertised is listed in their catalog as:

*"(Name of product) No. ...."*

### Spelling of Basic Products Having an "Amine" Group

The Council has expressed the opinion that the names of products which are basic and contain an "amine" group should end with the letter "e" and that the names of these products should also contain, if indicated, the additional term "hydrochloride" or "sulfate." Scientific nomenclature, in general, indicates a product with a name ending in "in" alone to be glucosidal in nature, whereas the ending "ine" would indicate that the compound is of a basic character. This style of nomenclature conforms with that adopted by scientific societies such as the U. S. Pharmacopeia, the American Chemical Society and the American Society of Biological Chemists. For the past few years the Council has required adoption of this style of nomenclature for new products submitted to it; and, for the sake of uniformity it urges adoption of the final "e," where needed, for old products as well. The Council asked all firms to cooperate in adopting this style of nomenclature and revise the names of their products which are basic and contain an "amine" group to include the final "e."

### Advertising Brochures

The Council will continue to examine reasonably brief advertising brochures in the light of permissible claims. The Council does not possess the facilities for adequate and detailed examination of onerously voluminous brochure material. In such cases the responsibility for any claims made must be accepted by the firm, which, by reason of the acceptance of its product, is bound to limit its claims to those sanctioned by the Council.

### Uniform Spelling of "Ampul" and "Ampuls"

The Council voted to adopt the uniform spelling "Ampul" and "Ampuls" whenever reference is made in its publications to this form of container. This spelling will apply in all instances except the names of accepted preparations in the title of which the firm uses a different spelling. In such instances the Council has requested that an effort be made to obtain conformity with the preferred spelling but failure to effect the change will not be held as a bar to Council acceptance of a drug.

### Enteric Coated Forms of Diethylstilbestrol and Digitalis

The Council will not consider or accept any enteric coated dosage forms of diethylstilbestrol or digitalis unless satisfactory evidence is submitted to show that they possess advantageous properties. There appears to be no evidence that enteric coated forms are superior to the plain dosage forms either from the standpoint of stability, therapeutic efficiency, or incidence of toxicity symptoms.

### Mineral Waters

The Council considers that artificial mineral waters are non-essential modifications of natural waters, and that natural mineral waters are only one feature prescribed by spas and health resorts. Mineral waters bottled for individual use are not eligible for acceptance, since there is no convincing evidence of the validity of the many therapeutic claims which are made for these preparations.

### Nasal Inhalant Preparations Containing Petrolatum

For several years brands of nasal inhalant preparations marketed in oily or ointment vehicles, consisting wholly or in part of petrolatum (principally liquid petrolatum) were included in *New and Nonofficial Remedies*. The Council reviewed the status of such preparations and is of the opinion that the repeated use of nasal inhalant preparations containing a vehicle of liquid petrolatum may lead to undesirable effects and is especially dangerous from the standpoint of lipid pneumonia; furthermore that inhalant preparations containing petrolatum offer no indispensable advantages over similar preparations containing vehicles of vegetable oils. The Council therefore omitted from N. N. R. all brands of inhalant nasal preparations containing petrolatum because of the danger of lipid pneumonia from repeated intranasal use and the fact that other safer vehicles for inhalant preparations are available. The Council has retained in N. N. R. only those oily inhalants which do not contain petrolatum, pending the development of more positive evidence concerning the irritative properties of other types of oils.

### 10 Per Cent Solutions of Sodium Morrhuate Not Acceptable

For some time the Council recognized the use of solutions of sodium morrhuate as a sclerosing agent for the injection treatment of varicose veins, and both 5 per cent and 10 per cent



solutions in combination with a local anesthetic were accepted for inclusion in *New and Nonofficial Remedies*. After due consideration of the available information, the Council voted to omit all accepted brands of the 10 per cent solution of sodium morrhuate because of its questionable utility and because serious accidents have followed the use of the stronger solution in the treatment of varicose veins.

The Council authorized a revision of N. N. R. to include a recommendation for the use of a preliminary test dose as a precaution against untoward reactions with 5 per cent solutions.

### Avoidance of "Split Titles" on Labels

Several instances have arisen in which the Council has been asked to give an opinion concerning the formulation of titles on labels. The following forms are submitted as examples:

SYNTHETIN  
(Reg. U. S. Patent Office)  
HYDROCHLORIDE

SYNTHETIN  
Brand of—(generic name)  
HYDROCHLORIDE

The Council ruled that the splitting of names was objectionable, in that it might lead to confusion on the part of physicians and pharmacists, and should therefore be avoided. It was recommended that the labels given above be revised as follows:

SYNTHETIN HYDROCHLORIDE  
(Synthetin is registered in the U. S. Patent Office)

SYNTHETIN\* HYDROCHLORIDE

\*BRAND OF—(GENERIC OR CHEMICAL NAME)

### Therapeutic Agents Derived from Animal Sources for Parenteral Use

The Council has considered the reasonable possibility that the use of therapeutic agents derived from animal sources may precipitate allergic reactions in individuals who have an allergic susceptibility to certain animals. Such allergic reactions would be most likely to occur in the use of noncrystalline preparations for parenteral use. Therefore the Council recommended that the source of animal products be declared on the label for accepted brands of noncrystalline products for parenteral injection and products for local application on freshly denuded surfaces, these to include preparations of liver extract, parathyroid solution, and thromboplastic substances. This may also be applied in the future to other preparations where evidence indicates the possibility of allergic reaction.

### Variations in Labeled Content of Accepted Preparations

Preparations varying beyond 5 per cent, plus or minus, of labeled content will be accepted only if such variation may be especially justified.

**Definition of "Label" and "Labeling"**

The Council voted to adopt the definition of the Federal Food, drug and Cosmetic Act of "label" and "labeling," which is given as follows:

The term "label" means a display of written, printed or graphic matter upon the immediate container of any article.

The term "labeling" means all labels and other written, printed or graphic matter upon any article or any of the containers or wrappers accompanying such article.



## The Council and Official Agencies

### The Relation of the Council to Other Bodies and to Governmental Agencies Regulating Drug Products and Their Advertising

There are several official and quasi-official bodies concerned with standards, distribution, labeling and advertising of drug products. The Council on Pharmacy and Chemistry, a voluntary group with no official standing, has since its formation cooperated closely with these agencies whose objectives are similar to those of the Council. In order that the functions of these agencies may be understood and their spheres of influence as they pertain to therapeutic agents defined, the following brief descriptions of their organizations and duties are given:

*The Food and Drug Administration:* This agency is part of the Federal Security Agency and is charged with the enforcement of the Federal Food, Drug and Cosmetic Act, the Caustic Poison Act, and several other statutes. The Food and Drug Administration is directed by the Commissioner of Foods and Drugs and maintains district offices in New York, Chicago and San Francisco, and station offices in Boston, Buffalo, New York, Philadelphia, Baltimore, Atlanta, Cincinnati, St. Louis, Chicago, New Orleans, Kansas City, Minneapolis, Denver, Los Angeles, San Francisco and Seattle. The administrative offices and special laboratories are located in Washington.

The Federal Food, Drug and Cosmetic Act regulates the labeling of drug products, but its authority does not extend to advertising. Seizure of offending goods, or criminal prosecution of responsible firms or persons in federal courts are among the methods used to enforce the provisions of the Act. In addition, repeated violations may be enjoined by the courts.

Violations may consist of either adulteration or misbranding or both. Adulteration refers to illegal deviations in composition of an article whereas misbranding refers to illegal statements made in the labeling or required statements omitted from the labeling.

Labeling refers not only to the labels on the immediate containers of drugs but also to circulars, pamphlets, brochures, etc., which accompany the article either physically or as a result of coming to rest with the article in the hands of the consumer.

The Food, Drug and Cosmetic Act prohibits certain things from appearing in the labeling, i.e., any statement which is false or misleading. It also requires certain things to appear in the

labeling, i.e., a statement of the quantity of contents, the name and address of the manufacturer or distributor, the name and quantity of certain specific narcotic or habit-forming drugs together with a statement "Warning: May be habit-forming," the common or usual name of each active ingredient and the quantities of certain specified ingredients, adequate directions for use unless exempted by regulation in which case the label must bear the statement "Caution, to be dispensed only by or on the prescription of a physician," and adequate warnings against possible misuse. The Act further prohibits the distribution of drugs which may be dangerous to health under the conditions of use prescribed or recommended in the labeling or of drugs which are deceptively packaged. New drugs may not be introduced into interstate commerce unless an application has been permitted to become effective. Such an application must show by adequate scientific evidence that the drug is safe for use under the conditions proposed for its use.

Certain drugs, namely, insulin, penicillin, and streptomycin, are subject to special control. Samples of each batch of these drugs are examined by the Food and Drug Administration for compliance with standards set forth in regulations issued by the Administration. Each batch must be certified as complying with these standards before the batch may be distributed. Such batches of these drugs are referred to as "certified drugs."

*The Federal Trade Commission:* The Federal Trade Commission is an independent agency of the Federal Government directly responsible to the President. The Commission administers several laws, the principal one being the Federal Commission Act. The principal provisions of this act have to do with the regulation of trade practices.

The Federal Trade Commission is composed of five members, appointed by the President. Not more than three of the members may be of any one political party, and the members serve for seven year terms. The work of the Commission is organized under divisions, and that having to do with drug products is known as the Medical Advisory Division.

The principal power of the Federal Trade Commission with respect to drugs lies in section 15 of the Federal Trade Commission Act which was amended by the Wheeler-Lea Act in 1938 giving the Commission control over the advertising of Foods, Drugs, and Cosmetics. Although the Commission has broad power to prevent the dissemination of false or misleading advertising to the general public, this power is circumscribed with respect to advertisements directed to the medical profession. The Act states "No advertisement of a drug shall be deemed to be false if it is disseminated only to members of the medical profession, contains no false representations of a material fact, and includes, or is accompanied in each instance by truthful disclosure of, the formula showing quantitatively each ingredient of such drug."

The enforcement of the Federal Trade Commission Act rests with the Commission. Trial of issues involved in violations is held before a Trial Examiner who reports his findings to the Commission. Final disposition of the case rests with the Commission. Violations of Commission "cease and desist" orders or appeals from Commission orders are considered by the Federal Courts. In many instances, controversies may be settled by stipulations between the Commission and respondents.

*The United States Public Health Service:* Among the many functions of the United States Public Health Service is the regulation of biological products. The Division of Biologics Control of the National Institute of Health administers that part of the Public Health Service Act of 1944 which incorporates the former Viruses, Serums, Toxins and Analogous Products Act.

The control exercised by the Public Health Service Act extends only to biologic products which are defined as "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man." By further definition, the term "biologic products" is extended to cover trivalent arsenical compounds. Pentavalent arsenical compounds are controlled under the Federal Food, Drug, and Cosmetic Act by administrative agreement between the Public Health Service and the Food and Drug Administration.

The control exercised by the Public Health Service over biologic products is through the inspection and licensing of establishments producing such products and by the examination and licensing of the products themselves. It is illegal, therefore, to produce any biologic product in an establishment which has not been duly licensed by the Public Health Service or to ship in interstate commerce any biologic product for which a license has not been issued and which is not effective at the time of shipment.

In order for a biologic product to be licensed under the provisions of the Public Health Service Act, it must meet the standards prescribed by the Division of Biologics Control of the National Institute of Health, and each batch must be tested for compliance with these standards. The labels of these products must bear the proper name of the product, the name, address, and license number of the manufacturer, the lot number, and the expiration date. Under certain conditions, and in the case of certain products, additional information may be required to appear on the label.

*The United States Treasury Department:* The Bureau of Narcotics of the United States Treasury Department administers the Harrison Narcotic Act. This Act is part of the Internal Revenue Code and is primarily a taxing measure. The Act provides for the payment of certain taxes and the affixing of revenue stamps to lots of narcotic drugs.

Under the Harrison Narcotic Act, opium, cocoa leaves, or any derivatives thereof or marihuana or any derivative thereof

is defined as being subject to the Act. Furthermore, by an amendment passed in 1946, the President may proclaim a drug as addiction-forming or addiction-sustaining upon a finding by the Secretary of the Treasury after due notice and an opportunity for a public hearing, and bring such a drug within the purview of the Harrison Narcotic Act. Under this provision, the drug Methadon(amidone) was proclaimed subject to the Act on July 31, 1947.

Although a tax measure, the Harrison Narcotic Act prescribes rigid controls over the transportation and distribution of narcotic drugs. Only physicians duly licensed under this Act may prescribe these drugs, and the form of such prescriptions and their handling is set forth in considerable detail.

*The Post Office Department:* The Fraud section of the post office under the direction of the Solicitor enforces the law pertaining to the fraudulent use of the mails. The use of the United States mails is a privilege and not a right and may be denied to those who use it for the purpose of defrauding the public. Therefore, the solicitation of customers and the shipping via the mails of drugs for which fraudulent claims are made may be the basis for the issuance of a "fraud order" and the suspension of all mail service to the guilty party. Determination of the guilt is made by the Solicitor after a hearing before him in which the facts are presented. Repeated violations or efforts to avoid compliance with such fraud orders may lead to criminal prosecution in the Federal Courts.

*The United States Pharmacopoeial Convention:* Under the General Committee on Revision, the United States Pharmacopoeial Convention issues at five-year intervals (formerly ten-year intervals) the United States Pharmacopoeia. The United States Pharmacopoeial Convention is a private body composed of representatives from medical schools, pharmacy schools, state medical associations, state pharmaceutical associations, the American Medical Association, the American Pharmaceutical Association, the American Chemical Society, and many other scientific and trade associations and also various interested federal bureaus and departments.

Under authority of the Federal Food, Drug, and Cosmetic Act, the United States Pharmacopoeia is an official standard for the products described therein. Products are accepted for inclusion in the Pharmacopoeia by the Committee on Revision on the basis of demonstrated therapeutic value or pharmaceutical necessity.

*The American Pharmaceutical Association:* The National Formulary is issued by the Committee on the National Formulary elected by the Council of the American Pharmaceutical Association. Admission of products to the National Formulary is based upon therapeutic value as well as upon the extent of use of the drug and the apparent need for official standards of certain drugs not necessarily widely used.

Under authority of the Federal Food, Drug and Cosmetic Act, the National Formulary is an official compendium, and

drugs described therein must meet the standards set forth in that publication.

## Preparations Specially Exempted from Council Consideration

The following official preparations have been declared exempt from Council consideration for inclusion in *New and Nonofficial Remedies*, as their actions, uses and nature are sufficiently well understood by physicians not to require such inclusion, although they have not had official status for more than 20 years which ordinarily exempts such articles from consideration.

Acetylsalicylic Acid  
 Ammonium Chloride  
 Antimeningococcic Serum  
 Caffeine with Sodium Benzoate  
 Calcium Gluconate  
 Carbon Dioxide  
 Chlorinated Paraffin (Chlorcosane)  
 Cinchophen  
 Dextrose Solution  
 Digitalis Preparations included in U. S. P.  
 Emetine Hydrochloride  
 Ferrous Sulfate  
 Ichthammol Preparations  
 Iron and Ammonium Citrates  
 Isotonic Solution of Three Chlorides  
 Lactated—Ringer's Solution  
 Liver and Stomach Preparations included in U. S. P.  
 Magnesium Sulfate  
 Magnesium Trisilicate  
 Methylene Blue  
 Natural Oil of Sweet Birch (Methyl Salicylate)  
 Neocinchophen  
 Oxygen  
 Oxygen-Carbon Dioxide Mixtures  
 Papaverine Hydrochloride  
 Pentobarbital Sodium  
 Quinine and Urea Hydrochloride  
 Salicylic Acid  
 Sodium Biphosphate  
 Isotonic Sodium Chloride Solution  
 Sodium Citrate  
 Sodium r-Lactate One-Sixth Molar  
 Sodium Salicylate  
 Strophanthin  
 Totaquine  
 Tribasic Calcium Phosphate  
 Tribasic Magnesium Phosphate  
 Trioxymethylene (Paraformaldehyde U. S. P. X)



## Table of Metric Doses with Approximate Apothecary Equivalents

The approximate dose equivalents in the following table represent the quantities which would be prescribed, under identical conditions, by physicians trained, respectively, in the metric or in the apothecary system of weights and measures.

When prepared dosage forms such as tablets, capsules, pills, etc. are prescribed in the metric system, the pharmacist may dispense the corresponding approximate equivalent in the apothecary system, and vice versa. This does not, however, authorize the alternative use of the approximate dose equivalents given below for specific quantities on a prescription which requires compounding, nor in converting a pharmaceutical formula from one system of weights or measures to the other system; for such purposes exact equivalents must be used (see U. S. P. XIII Table, page 913).

<i>Weights</i>	
Metric	Approximate Apothecary Equivalents
30 Gm. =	1 ounce
15 Gm. =	4 drachms
10 Gm. =	2½ drachms
7.5 Gm. =	2 drachms
6 Gm. =	90 gr.
5 Gm. =	75 gr.
4 Gm. =	60 gr. (1 drachm)
3 Gm. =	45 gr.
2 Gm. =	30 gr. (½ drachm)
1 Gm. =	15 gr.
0.75 Gm. =	12 gr.
0.6 Gm. =	10 gr.
0.5 Gm. =	7½ gr.
0.45 Gm. =	7 gr.
0.3 Gm. =	5 gr.
0.25 Gm. =	4 gr.
0.2 Gm. =	3 gr.
0.15 Gm. =	2½ gr.
0.12 Gm. =	2 gr.
0.1 Gm. =	1½ gr.
75 mg. =	1¼ gr.
60 mg. =	1 gr.
50 mg. =	¾ gr.
40 mg. =	⅔ gr.
30 mg. =	½ gr.
25 mg. =	⅜ gr.
20 mg. =	⅙ gr.
15 mg. =	¼ gr.
12 mg. =	⅓ gr.
10 mg. =	⅙ gr.

## Table of Metric Doses with Approximate Apothecary Equivalents—Continued

### *Weights*

Metric	Approximate Apothecary Equivalents
8 mg. =	$\frac{1}{8}$ gr.
6 mg. =	$\frac{1}{10}$ gr.
5 mg. =	$\frac{1}{12}$ gr.
4 mg. =	$\frac{1}{16}$ gr.
3 mg. =	$\frac{1}{20}$ gr.
1.5 mg. =	$\frac{1}{40}$ gr.
1 mg. =	$\frac{1}{60}$ gr.
0.8 mg. =	$\frac{1}{60}$ gr.
0.6 mg. =	$\frac{1}{100}$ gr.
0.5 mg. =	$\frac{1}{120}$ gr.
0.4 mg. =	$\frac{1}{150}$ gr.
0.3 mg. =	$\frac{1}{200}$ gr.
0.25 mg. =	$\frac{1}{250}$ gr.
0.2 mg. =	$\frac{1}{300}$ gr.
0.15 mg. =	$\frac{1}{400}$ gr.
0.1 mg. =	$\frac{1}{600}$ gr.

### *Liquid Measures*

Metric	Approximate Apothecary Equivalents
1000 cc. =	1 qt.
750 cc. =	1½ pt.
500 cc. =	1 pt.
250 cc. =	8 fl. oz.
200 cc. =	7 fl. oz.
100 cc. =	3½ fl. oz.
50 cc. =	1¾ fl. oz.
30 cc. =	1 fl. oz.
15 cc. =	½ fl. oz.
10 cc. =	2½ fl. drachm
8 cc. =	2 fl. drachm
5 cc. =	
4 cc. =	1 fl. drachm
3 cc. =	45 min.
2 cc. =	30 min.
1 cc. =	15 min.
0.75 cc. =	12 min.
0.6 cc. =	10 min.
0.5 cc. =	8 min.
0.3 cc. =	5 min.
0.25 cc. =	4 min.
0.2 cc. =	3 min.
0.1 cc. =	1½ min.

*NOTE*—A cubic centimeter (cc.) is the approximate equivalent of a milliliter (ml.).

The Council on Pharmacy and Chemistry has voted to use exclusively the metric system in any publication for which it

has sole responsibility. For this reason a table of equivalents will be provided in each book for those who are familiar only with the apothecary system.

Formerly almost every country had its own system of weights and measures, a practice which resulted in much confusion. The one system which is used almost universally and exclusively in the exact sciences is the metric system, which is based on the decimal system and has for its units the meter and the gram. Other systems still enjoying some popularity, albeit decreasing popularity, are the Apothecaries' or Troy weight, which is used in prescriptions, the Avoirdupois or Imperial Weight, which is used in commerce, and the United States Apothecaries' or Wine Measure, which is not to be confused with the British Imperial System. Examples of the denominations of each system are: Apothecaries—grain, scruple (20 grains), drachm (or dram, 60 grains) Troy ounce (480 grains or 8 drachms); Avoirdupois—grain, ounce (437½ grains), pound (16 ounces or 7,000 grains) and the ton (2,000 pounds); Wine Measure—minim, fluidrachm (60 minims), Fluidounce (8 fluidrachms or 480 minims), pint (16 fluidounces), quart (32 fluidounces). For fairly accurate conversion:

1 Gm.	= 15.43 grains
1 Gm.	= 0.2572 dram
1 Gm.	= 0.03215 Troy ounce
1 Gm.	= 0.03527 Avoirdupois ounce
1 Gm.	= 0.0022 Avoirdupois pound
1 grain	= 0.0648 gram (Gm.)
1 grain	= 64.8 milligrams (mg.)
1 dram	= 3.888 grams (Gm.)
1 Troy or Apothecary ounce	= 31.1 grams (Gm.)
1 Avoirdupois ounce	= 28.35 grams (Gm.)
1 Avoirdupois pound	= 453.6 grams (Gm.)
1 cubic centimeter	= 16.23 minims
1 milliliter	= 16.23 minims
1 milliliter	= 0.2705 fluid dram
1 milliliter	= 0.0338 fluid ounce
1 milliliter	= 0.00211 pint
1 milliliter	= 0.000264 gallon
1 minim	= 0.06161 cubic centimeters (cc.)
1 fluid dram	= 3.6966 cubic centimeters (cc.)
1 fluid ounce	= 29.57 cubic centimeters (cc.)
1 pint	= 473 cubic centimeters (cc.)

This degree of exactness, however, is not usually necessary in figuring dosages, and round figures are used in the accompanying tables of approximate equivalents, which will be found more convenient for translating dosages from one system to the other. However, further approximation by the use of household units may cause greater errors; every one should remember that a *minim* does not necessarily equal one drop; a drop will vary with the viscosity and surface tension of the fluid and the nature of the dropping container. A teaspoon will hold from 4 cc. (1 fluid dram) to 7 cc., a dessert spoon from 9 to 14 cc., a

tablespoon from 15 to 22 cc., a wine glass from 50 to 90 cc., a teacup from 125 to 240 cc. and a tumbler from 200 to 300 cc.

The following table of approximations may be convenient for translating pounds into kilograms:

11 pounds = 5 kilograms	110 pounds = 50 kilograms
22 pounds = 10 kilograms	132 pounds = 60 kilograms
33 pounds = 15 kilograms	154 pounds = 70 kilograms
44 pounds = 20 kilograms	176 pounds = 80 kilograms
55 pounds = 25 kilograms	198 pounds = 90 kilograms
66 pounds = 30 kilograms	220 pounds = 100 kilograms
88 pounds = 40 kilograms	242 pounds = 110 kilograms



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## SECTION A

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### CHAPTER I

## Agents Used in Allergy

This chapter includes agents used primarily in the diagnosis or treatment of allergic conditions. It thus comprises antigenic extracts used for the determination of sensitivity and for desensitization to specific allergens and also therapeutic agents that are capable of controlling allergic phenomena. The latter include histamine-antagonizing compounds that have been found clinically useful against certain manifestations of allergy. Sympathomimetic agents of value for this purpose are described in the chapter on Autonomic Drugs.

### Allergenic Preparations

Allergenic preparations are extracts, or solutions of various substances to which patients may become sensitive. These preparations are used for diagnosis, prophylaxis or "desensitization" in conditions due to hypersensitiveness. Some preparations have been claimed to give satisfactory results when used as a form of treatment. They are made from pollens; from hair, epidermis of animals, or feathers; from foods; from animal or vegetable fibers used in clothing or in upholstery; from plants, fungi, bacteria, and from a variety of other substances to which patients may become sensitive. In general a preparation is acceptable if from a single source, for example, from the epidermis or hair of a single animal; but mixtures of grass pollens and of ragweed pollens and of other closely related pollens have been accepted where their use has appeared rational.

Allergenic preparations may be divided into two classes: (a) those that produce a reaction when applied to the surface of the skin or mucous membranes; (b) those which ordinarily give rise to reaction when introduced internally. Sensitivity to substances in class (a) may often be determined by means of the so-called patch test. Sensitivity to substances in class (b) may often be determined by the so-called scratch test or by intradermal administration.

Solutions of allergens may deteriorate with age so it is necessary that they be used before the expiration of a given time determined by the regulations of the Federal Security Agency, and must be stored at a low temperature. To insure sterility, the council requires that liquid extracts shall be prepared so

as to avoid contamination and that their sale shall be authorized by the Federal Security Agency under the law governing the sale of biologic products. The council requires that the identity of any preservative used in accepted allergenic preparations be declared on the label.

**Actions and Uses.**—Allergenic preparations may be used for prophylaxis in instances of hay fever or pollen asthma by employing a series of suitably graded doses of specific pollen extracts up to and through the hay fever season, or for the treatment of hay fever by intracutaneous inoculation with suitable doses. In perennial asthma or rhinitis, if the offending substance can be determined by history or skin tests, patients may be treated by subcutaneous inoculations. Extracts of foods may be used to determine specific sensitivities to food but are not satisfactory for the treatment of these sensitivities.

**Dosage.**—No uniform method of standardization has been adopted. Two methods are acceptable, first standardization by the nitrogen content of the extract, and second standardization by amount of pollen or protein in the extract. The sensitivity of various patients is extremely variable so that the tolerance varies widely. For treatment graduated series of doses are supplied by the manufacturer. Most patients tolerate these standardized graduated doses, but in order to avoid untoward reactions at the beginning of the series, 0.02 cc. of the weakest solution should be injected intracutaneously before the series is begun. There should be no reaction or only a minimal wheal following this test.

Cutaneous tests, whether scratch, patch or intradermal, should be performed in accordance with an accepted procedure, and the interpretation of any such tests should only be undertaken by an individual who has had adequate experience under a competent instructor.

## Food, Epidermal and Other Extracts

### THE ARLINGTON CHEMICAL COMPANY

**Food, Epidermal and Incidental Allergens:** All of the items in lists A and B are marketed, for cutaneous testing, in vials containing: For foods and incidentals, 50 mg.: for epidermals, 25 mg.: and for furs, 15 mg. of dry allergens. In addition, the items in list A are marketed as extracts in hyposensitization sets of four 5 cc. vials, one each of four concentrations. In the case of food and dust extracts, these concentrations are 1:10,000, 1:5,000, 1:1,000 and 1:500. In the case of epidermal and incidental extracts, the concentrations are 1:100,000, 1:10,000, 1:1,000 and 1:500. Concentrations of 1:500 (and stronger solutions of certain items) are also marketed in 5 and 10 cc. vials. For intradermal testing 1, 3, 5 and 10 cc. vials of 1:500 solutions are available.

**List A—Foods:** *Almond*,<sup>1</sup> *Apple*,<sup>4</sup> *Apricot*,<sup>4</sup> *Asparagus*,<sup>19</sup> *Banana*,<sup>19</sup> *Barley*,<sup>19</sup> *Bass (Sea)*,<sup>2</sup> *Bean*,<sup>19</sup> *Beef*,<sup>18</sup> *Beet*,<sup>19</sup> *Blackberry*,<sup>5</sup> *Black-Eyed Pea*,<sup>19</sup> *Black Walnut*,<sup>1</sup> *Bluefish*,<sup>2</sup> *Bran (wheat)*,<sup>19</sup> *Brazil Nut*,<sup>1</sup> *Broccoli*,<sup>19</sup>

Brussel Sprouts,<sup>19</sup> Buckwheat,<sup>19</sup> Cabbage,<sup>19</sup> Cantaloupe,<sup>4</sup> Carp,<sup>2</sup> Carrot,<sup>4</sup>  
 Casein,<sup>17</sup> Cashew Nut,<sup>1</sup> Cauliflower,<sup>19</sup> Celery,<sup>19</sup> Cheese (American),<sup>8</sup>  
 Cheese (Roquefort),<sup>8</sup> Cheese (Swiss),<sup>8</sup> Cherry,<sup>19</sup> Chicken,<sup>18</sup> Cinnamon,<sup>19</sup>  
 Clam (Hard),<sup>2</sup> Clam (Soft),<sup>2</sup> Cocoa,<sup>19</sup> Coconut,<sup>1</sup> Codfish,<sup>2</sup> Coffee,<sup>19</sup>  
 Corn,<sup>19</sup> Crab,<sup>2</sup> Cranberry,<sup>19</sup> Cucumber,<sup>4</sup> Date,<sup>5</sup> Duck,<sup>18</sup> Egg Plant,<sup>4</sup> Egg-  
 white,<sup>7</sup> Egg (whole),<sup>18</sup> Egg (yolk),<sup>8</sup> Fig,<sup>5</sup> Flounder,<sup>2</sup> Garlic,<sup>19</sup> Gelatin,<sup>7</sup>  
 Ginger,<sup>19</sup> Goose,<sup>18</sup> Grape (Raisin),<sup>4</sup> Grapefruit,<sup>4</sup> Haddock,<sup>2</sup> Halibut,<sup>2</sup>  
 Herring,<sup>2</sup> Hops,<sup>19</sup> Lactalbumin,<sup>6</sup> Lamb,<sup>18</sup> Lemon,<sup>4</sup> Lettuce,<sup>19</sup> Lima  
 Bean,<sup>19</sup> Liver (Bovine),<sup>18</sup> Lobster,<sup>2</sup> Mackerel,<sup>2</sup> Malt,<sup>18</sup> Milk (Cow),<sup>7</sup>  
 Milk (Goat),<sup>7</sup> Mushroom,<sup>19</sup> Mustard,<sup>19</sup> Oat,<sup>19</sup> Olive,<sup>19</sup> Onion,<sup>19</sup> Orange,<sup>4</sup>  
 Oyster,<sup>2</sup> Paprika,<sup>19</sup> Parsley,<sup>19</sup> Pea,<sup>19</sup> Peach,<sup>4</sup> Peanut,<sup>1</sup> Pear,<sup>19</sup> Pecan,<sup>1</sup>  
 Pepper (Black),<sup>19</sup> Pepper (red and green),<sup>4</sup> Perch,<sup>2</sup> Pike,<sup>2</sup> Pineapple,<sup>19</sup>  
 Pork,<sup>18</sup> Potato,<sup>19</sup> Prune (Plum),<sup>4</sup> Pumpkin,<sup>4</sup> Quince Seed,<sup>4</sup> Radish,<sup>4</sup>  
 Raspberry,<sup>5</sup> Rhubarb,<sup>4</sup> Rice,<sup>19</sup> Rye,<sup>19</sup> Sage,<sup>19</sup> Salmon,<sup>2</sup> Sardine,<sup>2</sup> Scallop,<sup>18</sup>  
 Shad,<sup>2</sup> Shrimp,<sup>2</sup> Smelts,<sup>2</sup> Sole,<sup>2</sup> Soy Bean,<sup>19</sup> Spinach,<sup>19</sup> Squash,<sup>19</sup>  
 Strawberry,<sup>5</sup> String Bean,<sup>19</sup> Sweet Potato,<sup>19</sup> Swordfish,<sup>2</sup> Tangerine,<sup>4</sup>  
 Tea,<sup>19</sup> Thyme,<sup>19</sup> Tomato,<sup>4</sup> Trout (sea),<sup>2</sup> Tuna fish,<sup>2</sup> Turkey,<sup>18</sup>  
 Turnip,<sup>4</sup> Vanilla,<sup>4</sup> Veal,<sup>18</sup> Walnut (English),<sup>1</sup> Watercress,<sup>19</sup>  
 Watermelon,<sup>4</sup> Wheat,<sup>8</sup> Wheat globulin,<sup>11</sup> Wheat protease,<sup>10</sup>  
 Whitefish (Lake),<sup>2</sup> Yeast<sup>19</sup>; Incidentals: Bee,<sup>19</sup> Castor Bean,<sup>1</sup>  
 Cotton Linters, Cotton Seed, Dust,<sup>14</sup> Flaxseed,<sup>4</sup> Glue,<sup>7</sup> Grain Mill  
 Dust,<sup>19</sup> Gum Acacia (Arabic),<sup>8</sup> Gum Karaya,<sup>3</sup> Gum Tragacanth,<sup>3</sup> Horse  
 Serum,<sup>7</sup> Kapok,<sup>19</sup> Orris root,<sup>19</sup> Pyrethrum,<sup>2</sup> Sand fly,<sup>19</sup> Silk,<sup>14</sup> Tobacco<sup>19</sup>;  
 Epidermals: Camel Hair,<sup>14</sup> Cat Hair,<sup>14</sup> Cattle Hair,<sup>14</sup> Dog Hair,<sup>14</sup> Feath-  
 ers (Mixed),<sup>14</sup> Goat Hair,<sup>14</sup> Guinea Pig Hair,<sup>14</sup> Hog Hair,<sup>14</sup> Horse  
 Dander,<sup>14</sup> Human Hair,<sup>14</sup> Mouse Hair,<sup>14</sup> Rabbit Hair,<sup>14</sup> Rat Hair,<sup>14</sup>  
 Sheep Wool,<sup>14</sup>; List B—Foods: Allspice,<sup>19</sup> Artichoke,<sup>19</sup> Bass (Black),<sup>2</sup>  
 Blueberry,<sup>5</sup> Butterfish,<sup>2</sup> Calves' Brains,<sup>18</sup> Casaba,<sup>4</sup> Catfish,<sup>2</sup> Celery Cab-  
 bage (Petai),<sup>19</sup> Cheese (Camembert),<sup>8</sup> Cheese (Gorgonzola),<sup>8</sup> Cheese  
 (Limburger),<sup>8</sup> Cheese (Parmesan),<sup>8</sup> Chestnut,<sup>1</sup> Chick Pea or Garbanzo,<sup>19</sup>  
 Chicory,<sup>19</sup> Chili Pepper,<sup>4</sup> Chive,<sup>19</sup> Clove,<sup>19</sup> Collard,<sup>19</sup> Crab (Soft Shell),<sup>2</sup>  
 Crappie,<sup>2</sup> Crayfish,<sup>2</sup> Currant (Red),<sup>5</sup> Curry,<sup>19</sup> Dandelion,<sup>19</sup> Dill,<sup>4</sup> Duck  
 Egg,<sup>18</sup> Eel,<sup>2</sup> Endive,<sup>19</sup> Filbert (Hazelnut),<sup>1</sup> Frogs' Legs,<sup>2</sup> Goose Egg,<sup>18</sup>  
 Hickory,<sup>1</sup> Honeydew,<sup>4</sup> Horse Meat,<sup>18</sup> Horse Radish,<sup>19</sup> Kale,<sup>19</sup> Kidney  
 (Beef),<sup>19</sup> Kohl-rabi,<sup>19</sup> Leek,<sup>19</sup> Lentil,<sup>19</sup> Limes,<sup>4</sup> Liver (Chicken),<sup>18</sup>  
 Mace,<sup>19</sup> Mint,<sup>8</sup> Mullet,<sup>2</sup> Nutmeg,<sup>19</sup> Okra,<sup>4</sup> Olive (Ripe),<sup>19</sup> Papaya,<sup>19</sup>  
 Parsnip,<sup>19</sup> Pheasant,<sup>18</sup> Pickerel,<sup>2</sup> Pimento,<sup>4</sup> Pistachio nut,<sup>1</sup> Poppy seed,<sup>4</sup>  
 Porgy,<sup>2</sup> Rabbit,<sup>18</sup> Red Snapper,<sup>2</sup> Rutabaga,<sup>19</sup> Sesame,<sup>19</sup> Shad Roe,<sup>18</sup>  
 Squab,<sup>18</sup> Sturgeon,<sup>2</sup> Sweet Bread,<sup>18</sup> Swiss Chard,<sup>19</sup> Tongue (Beef),<sup>18</sup>  
 Trout Lake,<sup>2</sup> Turtle,<sup>2</sup> Venison,<sup>18</sup> Weakfish,<sup>2</sup> Wheat gliadin,<sup>12</sup> Wheat  
 glutenin,<sup>13</sup> Wheat leucosin<sup>9</sup>; Incidentals: Alfalfa Leaves,<sup>19</sup> Chiclé,<sup>8</sup>  
 Coddling Moth,<sup>19</sup> Derris Root,<sup>3</sup> Juniper,<sup>4</sup> Jute,<sup>19</sup> Licorice,<sup>19</sup> Lycopodium,<sup>20</sup>  
 Red Cedar,<sup>19</sup> Southern Moss<sup>19</sup>; Furs: Alaska Seal,<sup>14</sup> Beaver,<sup>14</sup> Fox,<sup>14</sup>  
 Muskrat (Hudson Seal),<sup>14</sup> Opossum,<sup>14</sup> Persian Lamb Squirrel,<sup>14</sup> (Caracul),<sup>14</sup> Skunk<sup>14</sup>; Smuts: Barley Smut,<sup>8</sup> Bunt of Wheat,<sup>8</sup> Corn Smut,<sup>8</sup>  
 Millet Smut,<sup>8</sup> Oat Smut,<sup>8</sup> Rye Smut,<sup>8</sup> Sorghum Smut,<sup>8</sup> Wheat Smut<sup>8</sup>.

Allergen extracts-Arlington, are prepared as follows: A weighed amount of the dried protein material, prepared as indicated below, is suspended in twentieth-normal sodium hydroxide solution. The suspension is centrifuged and decanted and the residue, if one remains, is exhausted by successive extractions with twentieth-normal sodium hydroxide solution. The extracts are combined and filtered until clear. To the filtrate is added one-fourth volume of a solution containing in each hundred cubic centimeters di-sodium phosphate ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ) 1.43 Gm. and mono-potassium phosphate ( $\text{KH}_2\text{PO}_4$ ) 0.363 Gm. The reaction of the resultant solution is then adjusted to pH 8.3 by the addition of either hydrochloric acid or sodium hydroxide solution. Cresol in the proportion of 0.4 per cent is added and the solution sterilized by filtration through Berkefeld filters. The finished products are tested for sterility according to the methods required by the U. S. Public Health Service. The protein content of the sterile solution is estimated by multiplying the nitrogen content, determined according to the Kjeldahl method, by the factor 6.25. From these finished extracts, necessary dilutions are prepared aseptically with a diluent of sterile phosphate buffer containing 0.4 per cent tricresol. The intermediate and finished dilution products are tested for sterility according to the methods required by the U. S. Public Health Service.



The dried protein material used in the preparation of the extracts marked 1 is prepared as follows: The hard shells are removed; nuts are ground and extracted with carbon tetrachloride or acetone to remove oils. The residue is extracted with tenth-normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 2 is prepared as follows: The edible portion is separated from the nonedible parts (scales, bones and so on) and finely ground. The material is then extracted with tenth-normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 3 is prepared as follows: The material is washed in acetone and ether and then ground and sifted.

The dried protein material used in the preparation of the extracts marked 4 is prepared as follows: The seeds are separated and the material chopped fine. An extract is made, sufficient tenth-normal sodium hydroxide solution being used to make the mixture alkaline to litmus. The extract is filtered and neutralized and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 5 is prepared as follows: The material is chopped and after mixing with thymol is spread on trays to dry. The dried material is ground fine and extracted with tenth-normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extract marked 6 is prepared as follows: Skimmed milk is diluted with two volumes of distilled water. Diluted hydrochloric acid is added until the casein settles out. The casein is filtered off and the filtrate neutralized and concentrated in vacuo. Ammonium sulfate is added to saturation point and the precipitate redissolved in distilled water.

The dried protein material used in the preparation of the extracts marked 7 is prepared as follows: The material is dissolved in or diluted with distilled water. The solution is filtered if necessary and the protein precipitated with acetone. The precipitate is washed with acetone, dried, ground and sifted.

The dried protein material used in the preparation of the extract marked 8 is prepared as follows: The five protein fractions present in and separately prepared from wheat flour are mixed.

The dried protein material used in the preparation of the extract marked 9 is prepared as follows: Wheat flour is extracted with distilled water. The extract is collected, filtered clear and made slightly acid. It is then heated to 65° C. and the precipitate filtered off, dried and sifted.

The dried protein material used in the preparation of the extract marked 10 is prepared as follows: The filtrate obtained after removing wheat leucosin is concentrated in vacuo. Four volumes of acetone are added and the resulting precipitate separated, dried, ground and sifted.

The dried protein material used in the preparation of the extract marked 11 is prepared as follows: Wheat flour is extracted with distilled water to remove the leucosin and protease; the residue remaining is then extracted with 10 per cent sodium chloride solution. The extract is placed in a dialyzer until the precipitate settles out. The precipitate is washed with water, dried and sifted.

The dried protein material used in the preparation of the extract marked 12 is prepared as follows: The residue of wheat flour remaining after the flour has been extracted with water and with 10 per cent sodium chloride solution is extracted with 80 per cent alcohol. The extract is concentrated in vacuo, dried, ground and sifted.

The dried protein material used in the preparation of the extract marked 13 is prepared as follows: Wheat flour is extracted with distilled water, 10 per cent sodium chloride solution and 80 per cent alcohol. The residue remaining is then extracted with tenth-normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 14 is prepared as follows: The material is extracted with tenth-normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the precipitate collected, dried and sifted. The filtrate is placed in a dialyzer until it is salt free and then concentrated in vacuo. The concentrate is precipitated with acetone, dried and sifted. Both fractions are then mixed.

The dried protein material used in the preparation of the extract marked 15 is prepared as follows: The material is dissolved in five volumes of distilled water and then centrifuged. The supernatant liquid is discarded; the residue is dried and powdered.

The dried protein material used in the preparation of the extracts marked 16 is prepared as follows: Equal parts of the egg white and egg proteins are mixed.

The dried protein material used in the preparation of the extract marked 17 is prepared as follows: Fresh skimmed milk is diluted with two volumes of distilled water. Diluted hydrochloric acid is added until the casein separates out. The casein is redissolved in sodium hydroxide solution and reprecipitated with diluted hydrochloric acid. It is then washed, dried, ground and sifted.

The dried protein material used in the preparation of the extracts marked 18 is prepared as follows: After removal of feathers, bones and the like, any excess fat is trimmed off. The meat is collected and chopped fine. The material is then extracted with tenth-normal sodium hydroxide solution. The extract is neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The dried protein material used in the preparation of the extracts marked 19 is prepared as follows: The material is chopped thoroughly or reduced to a fine powder by grinding. Where excess oil or fat is present, this is removed by treatment with acetone or carbon tetrachloride. The material is then extracted with tenth-normal sodium hydroxide solution. The extract is then neutralized with diluted hydrochloric acid and the resulting precipitate collected, dried and sifted.

The extracts marked 20 are prepared by the same method used in the preparation of pollen extracts-Arlington.

#### ENDO PRODUCTS, INC.

**Allergenic Extracts:** The following extract is marketed in treatment set packages of four 10 cc. vials containing, respectively, slightly more than 1 cc. of a 2.5 per cent, 0.25 per cent, 0.025 per cent and 0.0025 per cent dilution of the original extract in glycerosaline solution (50 per cent glycerin) and four 10 cc. vials containing 9 cc. of diluting fluid (0.4 per cent phenol in isotonic solution of sodium chloride); in maintenance treatment packages of one 10 cc. vial containing 1 cc. of a 2.5 per cent dilution of the original extract in glycerosaline solution (50 per cent glycerin) and one 10 cc. vial of diluting fluid (0.4 per cent phenol in isotonic solution of sodium chloride); in bulk treatment packages of 5 and 10 cc. containing a 2.5 per cent dilution of the original extract in glycerosaline solution (50 per cent glycerin). The extract is also supplied in special treatment packages of one 10 cc. vial containing 4 cc. of a 2.5 per cent dilution of the original extract in glycerosaline solution (50 per cent glycerin) and one 10 cc. vial containing 6 cc. of diluting fluid (0.4 per cent phenol in isotonic solution of sodium chloride).

#### *House Dust (Purified Concentrate).*

Allergenic extract house dust (purified concentrate)-Endo is prepared from dust obtained from mattresses and household furniture.

A mixture of 1 part by weight of house dust and 2 parts by volume of distilled water is covered with toluene and extracted while stirring,

at 0 to 5 C. for seventy-two hours. The aqueous extract is separated from the dust by centrifugation.

Three volumes of the water extract are cooled to 0 to 5 C. and treated with 2 volumes of previously cooled acetone. The precipitated material, separated by centrifugation, is discarded. Acetone is added to the clear centrifugate until a concentration of 75 per cent acetone is reached. The precipitated material is centrifuged and the liquid is discarded. Adhering acetone is blown off with cold dry air. The precipitate is taken up in one tenth the original volume of distilled water. Three volumes of this aqueous solution are treated with 2 volumes of acetone, mixed thoroughly and centrifuged. The liquid is reserved. The residue is washed with a small amount of a 40 to 60 per cent V/V acetone-water solution until the original volume of supernatant and wash liquids is equal to one tenth the original volume. Sufficient acetone is added to yield a 75 per cent concentration. The syrupy precipitate is separated by centrifugation and the adhering acetone is removed by cold dry air. The syrup is taken up with one tenth the original volume of distilled water and dialyzed against running distilled water until about 50 per cent of the total dissolved solids has been removed. To the 5 per cent solution w/v (adjusted by low temperature vacuum distillation if necessary), obtained by dialysis, sodium chloride is added (1.8 Gm. per hundred cubic centimeters) and the solution is passed through a Seitz filter. The sterile solution is added to an equal volume of previously sterilized glycerin. This solution of 2.5 per cent allergenic extract constitutes the stock solution from which appropriate dilutions are prepared. All diluted solutions are passed through a Seitz filter before filling into sterile vials by aseptic technic.

**Allergenic Extracts Diagnostic:** The following extract is marketed in packages of a single vial, with accompanying applicator containing 1 cc. of a 1:200 solution (0.5 per cent) of the original extract in 50 per cent glycerin.

*House Dust (Purified) Concentrate.*

This extract, for use by the scratch method and cutaneous testing, is prepared in much the same manner as the allergenic extract-Endo, for treatment, just described. The procedure is the same up to the point of dialysis, whereupon the extract for diagnosis undergoes the following treatment: To the solution obtained immediately before dialysis ammonium sulfate is added (60 Gm. per hundred cubic centimeters). The coagulated material is centrifuged. The separated solid is dissolved in one-half the original volume of distilled water and the ammonium sulfate precipitation is repeated. The solid separated by centrifugation is suspended in a small volume of water and dialyzed until the solution in the sac does not respond to tests for the sulfate ion. The dialyzed solution is centrifuged to remove a small amount of suspended solids and the solution is adjusted (by vacuum distillation at low temperature if necessary) to contain 1 per cent of dissolved solids. Sufficient sodium chloride is added to yield a 1.8 per cent solution with respect to sodium chloride. The solution is diluted with an equal volume of glycerin and filtered through a Seitz filter. This 0.5 per cent solution constitutes the allergenic extract purified house dust concentrate for diagnosis by scratch testing.

**HOLLISTER-STIER LABORATORIES**

**Allergenic Extracts Diagnostic:** Used in testing for sensitivities to foods, animal epidermals, fungi and miscellaneous factors (390 items) marketed in 1 cc. vials fitted with rubber bulb and glass dropper for scratch testing and rubber-capped vials for intradermal testing. The scratch testing extract is standardized on weight volume basis; the intradermal extract on a nitrogen basis (micro-kjeldahl method).

**Allergenic extracts—Hollister-Stier** for scratch testing are prepared by extracting for five days at 37° C. one part of the dried protein ma-

terial with ten parts of a menstruum which is composed of 50 per cent of glycerine by weight, 5 per cent of sodium chloride and 45 per cent of distilled water. The extract is clarified and sterilized by Seitz filtration. The finished product represents a 1 to 10 dilution of the original substance.

The material for intradermal testing is extracted in a buffered saline solution, containing 1-10,000 Merthiolate as a preservative. The extract is clarified and sterilized by Seitz filtration. The nitrogen content of the extract is determined and then diluted with buffered saline to the required strength.

#### PARKE, DAVIS & COMPANY

**Allergenic Extracts, Diagnostic:** Protein extracts derived from food, plant, bacterial and other proteins, in the form of paste, the base of which is a mixture of glycerin and glycerite of starch. One part of paste represents one part of original material. The extracts afford a convenient means of carrying out the diagnostic scratch test. They are supplied in collapsible tubes containing 1.5 Gm. of material, enough for approximately 50 tests.

**Group Allergenic Extracts, Diagnostic:** A mixture of equal parts of two or more protein extracts diagnostic-P. D. & Co., supplied in collapsible tubes containing 1.5 Gm. of the mixture. The protein constituents of each group are selected on the basis of their class relationships.

#### WYETH, INCORPORATED

**Protein Extracts Diagnostic:** These extracts for the diagnosis of protein sensitivity by the intracutaneous method are supplied in 1 cc. size cartridge ("Tubex") vials containing sufficient protein material of appropriate dilution for twenty to thirty tests. The test sets are accompanied by a suitable cartridge syringe, sterile needles and three cartridge vials each of epinephrine hydrochloride solution, buffered saline solution and distilled water. After injection of each extract the needle should be flushed with distilled water to avoid contamination with the extract used previously.

Extracts marketed in dilution representing 0.005 mg. of nitrogen per cubic centimeter:

*Apple,<sup>2</sup> Apricot,<sup>2</sup> Artichoke,<sup>2</sup> Asparagus,<sup>2</sup> Banana,<sup>2</sup> Beef,<sup>2</sup> Beets,<sup>2</sup> Blackberry,<sup>2</sup> Broccoli,<sup>2</sup> Cabbage,<sup>2</sup> Cantaloupe,<sup>2</sup> Carrot,<sup>2</sup> Cauliflower,<sup>2</sup> Celery,<sup>2</sup> Cherry,<sup>2</sup> Chicken,<sup>2</sup> Cucumber,<sup>2</sup> Dates,<sup>2</sup> Endive,<sup>2</sup> Fig,<sup>2</sup> Garlic,<sup>2</sup> Grape,<sup>2</sup> Grapefruit,<sup>2</sup> Green Pea,<sup>2</sup> Leeks,<sup>2</sup> Lemon,<sup>2</sup> Lentil,<sup>2</sup> Lettuce,<sup>2</sup> Mushroom,<sup>2</sup> Mutton,<sup>2</sup> Olive,<sup>2</sup> Onion,<sup>2</sup> Orange,<sup>2</sup> Parsley,<sup>2</sup> Peach,<sup>2</sup> Pear,<sup>2</sup> Pepper (Green),<sup>2</sup> Pineapple,<sup>2</sup> Plum,<sup>2</sup> Pork,<sup>2</sup> Potato (Sweet),<sup>2</sup> Potato (White),<sup>2</sup> Prune,<sup>2</sup> Pumpkin,<sup>2</sup> Radish,<sup>2</sup> Raspberry,<sup>2</sup> Rhubarb,<sup>2</sup> Spinach,<sup>2</sup> Squash,<sup>2</sup> Strawberry,<sup>2</sup> Tomato,<sup>2</sup> Turnip,<sup>2</sup> Watercress,<sup>2</sup> Watermelon.<sup>2</sup>*

Extracts marketed in dilutions representing 0.01 mg. of nitrogen per cubic centimeter:

*Alfalfa (Hay),<sup>4</sup> Bay Leaves,<sup>4</sup> Bran,<sup>4</sup> Chicken Feathers,<sup>4</sup> Cinnamon,<sup>4</sup> Clove,<sup>4</sup> Coffee,<sup>4</sup> Corn (Sweet),<sup>4</sup> Duck Feathers,<sup>4</sup> Ginger,<sup>4</sup> Goat Hair,<sup>4</sup> Goose Feathers,<sup>4</sup> Hops,<sup>4</sup> Kidney Bean,<sup>4</sup> Lactalbumin,<sup>4</sup> Milk (Cheeses),<sup>4</sup> Nutmeg,<sup>4</sup> Oats,<sup>4</sup> Rice,<sup>4</sup> Rice Powder,<sup>4</sup> Rye,<sup>4</sup> Tea,<sup>4</sup> Thyme,<sup>4</sup> Wheat,<sup>4</sup> Wool.<sup>5</sup>*

Extracts marketed in dilutions representing 0.005 mg. of nitrogen per cubic centimeter:

*Brasil Nut,<sup>4</sup> Cashew Nut,<sup>4</sup> Chestnut,<sup>4</sup> Cocoa (Chocolate),<sup>4</sup> Hazel Nut,<sup>4</sup> Hickory Nut,<sup>4</sup> Lima Bean,<sup>4</sup> Navy Bean,<sup>4</sup> Pea,<sup>4</sup> Pecan,<sup>4</sup> Pistachio,<sup>4</sup> Soy Bean,<sup>4</sup> String Bean.<sup>4</sup>*

Extracts marketed in dilutions representing 0.001 mg. of nitrogen per cubic centimeter:

*Alder,*<sup>4</sup> *Almond,*<sup>4</sup> *Anise Seed,*<sup>4</sup> *Ash (Oregon),*<sup>4</sup> *Ash (White),*<sup>4</sup> *Barley,*<sup>4</sup> *Bass,*<sup>3</sup> *Beaver,*<sup>5</sup> *Beech,*<sup>4</sup> *Bermuda Grass,*<sup>4</sup> *Birch,*<sup>4</sup> *Bluefish,*<sup>4</sup> *Camel Hair,*<sup>5</sup> *Caracul,*<sup>4</sup> *Cara-way Seed,*<sup>4</sup> *Carp,*<sup>3</sup> *Cat Hair,*<sup>5</sup> *Clam,*<sup>3</sup> *Cocklebur,*<sup>4</sup> *Cocoanut,*<sup>4</sup> *Cod,*<sup>3</sup> *Cotton Seed,*<sup>4</sup> *Cow Hair,*<sup>5</sup> *Crab,*<sup>3</sup> *Dog Hair,*<sup>5</sup> *Elm,*<sup>4</sup> *Ermine,*<sup>5</sup> *False Ragweed,*<sup>4</sup> *Flaxseed,*<sup>4</sup> *Flounder,*<sup>4</sup> *Fox,*<sup>5</sup> *Giant Ragweed,*<sup>4</sup> *Haddock,*<sup>3</sup> *Halibut,*<sup>3</sup> *Herring,*<sup>5</sup> *Hickory,*<sup>4</sup> *Hog Hair,*<sup>5</sup> *Horse Hair,*<sup>5</sup> *Johnson Grass,*<sup>4</sup> *June Grass,*<sup>4</sup> *Kapok Seed,*<sup>4</sup> *Lamb (Black),*<sup>5</sup> *Lamb (Persian),*<sup>5</sup> *Leopard,*<sup>5</sup> *Lobster,*<sup>3</sup> *Mackerel,*<sup>3</sup> *Maple,*<sup>4</sup> *Mink,*<sup>5</sup> *Muskral,*<sup>5</sup> *Nutria,*<sup>5</sup> *Oak,*<sup>4</sup> *Orchard Grass,*<sup>4</sup> *Orris Root,*<sup>4</sup> *Oyster,*<sup>3</sup> *Peanut,*<sup>4</sup> *Perch,*<sup>3</sup> *Pike,*<sup>3</sup> *Plantain,*<sup>4</sup> *Poplar,*<sup>4</sup> *Pyrethrum,*<sup>4</sup> *Rabbit,*<sup>5</sup> *Rabbit Hair,*<sup>5</sup> *Raccoon,*<sup>5</sup> *Ragweed,*<sup>4</sup> *Red-Top,*<sup>4</sup> *Russian Thistle,*<sup>4</sup> *Sagebrush,*<sup>4</sup> *Salmon,*<sup>3</sup> *Sardine,*<sup>3</sup> *Scallop,*<sup>3</sup> *Seal,*<sup>5</sup> *Shad,*<sup>3</sup> *Shrimp,*<sup>3</sup> *Silk,*<sup>4</sup> *Skunk,*<sup>5</sup> *Smelts,*<sup>3</sup> *Sole,*<sup>3</sup> *Squirrel,*<sup>5</sup> *Sweet Vernal Grass,*<sup>4</sup> *Sycamore,*<sup>4</sup> *Timothy,*<sup>4</sup> *Tobacco,*<sup>4</sup> *Trout,*<sup>3</sup> *Tuna,*<sup>3</sup> *Walnut,*<sup>4</sup> *Walnut (English),*<sup>4</sup> *Weasel,*<sup>5</sup> *Western Ragweed,*<sup>4</sup> *Wormwood,*<sup>4</sup> *Yeast.*<sup>4</sup>

Extracts marketed in dilutions representing 0.0005 mg. of nitrogen per cubic centimeter:

*Egg (Chicken),*<sup>7</sup> *Mustard,*<sup>4</sup> *Glue (Fish),*<sup>10</sup>

Extract marketed in dilutions of 1-10:

*House Dust.*

Extract marketed in dilutions of 1-100:

*Horse Serum.*<sup>9</sup>

Protein extracts diagnostic are prepared from the various substances by extraction with a slightly alkaline, buffered saline solution composed of sodium chloride, 0.5 per cent, sodium bicarbonate, 0.275 per cent and phenol 0.4 per cent, in distilled water. Carbon dioxide is then bubbled into the extracts until they become colorless when tested to phenolphthalein. The products are standardized on the basis of their nitrogen content per unit volume (Kjeldahl method). Certain products, namely house dust and horse serum, not lending themselves to such standardization are therefore marketed in dilutions of 1-10 and 1-100 respectively.

Extracts marked 1 are prepared by the following method: The juices are squeezed and separated from pulp by filtration. The pH is adjusted to 7.4 with sodium carbonate, diluted with buffered alkaline saline solution, filtered, standardized and diluted to appropriate strength.

Extracts marked 2 are prepared by the following method: The crude material is ground as fine as possible. Alkaline buffered solution is added to the pulp and allowed to extract under toluene for from one to two days at room temperature. After the toluene has been removed in a separator the extract is filtered, standardized and diluted to appropriate strength.

Extracts marked 3 are prepared by the following method: After the removal of all fat and tendons, the muscle fibers are then ground as fine as possible. The ground material is washed with warm (50 C.) toluene until entirely free of fats. The toluene washings are discarded and the ground meats are extracted under toluene with alkaline buffered saline solution at room temperature for from one to two days. The toluene is then removed in a separator and the extract is filtered, standardized and diluted to appropriate strength.

Extracts marked 4 are prepared by the following method: The materials are ground as fine as possible; the powder or flour is washed with ether and toluene until the washings are clear and colorless. The washings are discarded and the residue is dried. The dried residue is extracted with alkaline buffered saline solution under toluene at room temperature for from one to two days. The extract is filtered through a Buchner funnel and the toluene removed in a separator. The extract is filtered, standardized and diluted to appropriate strength.

Extracts marked 5 are prepared by the following method: The materials are washed with ether and toluene, dried and extracted under toluene for from one to two days at room temperature. The extract is cleared of toluene in a separator, filtered, standardized and diluted to appropriate strength.

Lactalbumin, marked 6, is prepared by the following method: The casein is precipitated with renin and the lactalbumin, after neutralization with sodium bicarbonate, is precipitated from the resulting whey with acetone. The lactalbumin is then extracted with alkaline buffered saline solution, filtered, standardized and diluted to appropriate strength.

Egg (Chicken), marked 7, is prepared by the following method: The white is separated from the yolk and diluted with alkaline buffered saline solution, filtered, standardized and diluted to appropriate strength.

House Dust, marked 8, is prepared by the following method: The dust is defatted with ether and toluene, dried, extracted with alkaline buffered saline solution, dialyzed, filtered and diluted to appropriate strength.

Horse Serum, marked 9, is prepared by the following method: Normal Horse Serum is treated with phenol, so that the final concentration of phenol is 0.4 per cent. It is then diluted to proper strength with alkaline buffered saline solution.

Glue (Fish), marked 10, is prepared by the following method: The glue is diluted in alkaline buffered saline solution standardized and diluted to appropriate strength with alkaline buffered saline solution.

## Fungus Extracts

### ABBOTT LABORATORIES

Fungus Extracts 5% : 2 cc., 5 cc., 10 cc. and 30 cc. vials.

*Alternaria spp.*; *Aspergillus fumigatus*; *Aspergillus niger* Group; *Cephalothecium roseum*; *Hormodendrum spp.*; *Monilia sitophila*; *Mucor spp.*; *Penicillium rubrum*; *Puccinia coronata avenae* (Crown Rust of Oats); *Ustilago avenae* (Loose Smut of Oats); *Ustilago tritici* (Loose Smut of Wheat) and *Ustilago medians* (Loose Smut of Barley); *Ustilago seae* (Corn Smut); Yeast.

The yeast extract is prepared from dried brewers' yeast; the *Alternaria spp.* extract is prepared from the dried mass of spores with its supporting mycelium; the other extracts are prepared from the dried spores alone. The material is extracted at room temperature with a menstruum, consisting of equal volumes of glycerin and a solution containing sodium chloride 5 Gm. and sodium bicarbonate 2.7 Gm. in distilled water 1,000 cc., for from four to five days and is clarified and sterilized by Berkefeld filtration. The finished liquid is a 5% W/V extract of the dried fungus material, each cubic centimeter representing 0.05 Gm. of dried material.

### THE ARLINGTON CHEMICAL COMPANY

**Fungus Allergens:** These preparations are marketed in vials containing 50 mg. of the dried fungi. In addition the items to follow are marketed as extracts for hyposensitization in 3, 5, and 10 cc. vials at concentrations 1:20, 1:100, 1:500, 1:1000, 1:5000, and 1:10,000. Treatment sets of five 3 cc. vials with one vial at each of the following concentrations 1:10,000, 1:5000, 1:1000, 1:500, 1:100 are also offered.

Extracts marketed in dry form, and in solution form:

*Achorion schoenleinii*; *Alternaria sp.*; *Aspergillus flavus*; *Aspergillus fumigatus*; *Aspergillus glaucus*; *Aspergillus nidulans*; *Aspergillus niger*; *Cephalosporium*; *Cephalothecium*; *Chaetomium sp.*; *Cladosporium*; *Epidermophyton inguinale*; *Fusarium*; *Helminthosporium*; *Hormodendrum*; *Microsporium lanosum*; *Monilia albicans*; *Monilia sitophila*; *Mucor plumbeus*; *Penicillium camemberti*; *Penicillium chrysogenum*; *Penicillium digitatum*; *Penicillium notatum*; *Penicillium roqueforti*; *Rhizopus*; *Trichoderma*; *Trichophyton gypsum*; and *Trichophyton interdigitale*.

In addition the following stock fungus mixtures are offered in solution form only.

*Aspergillus mixture*—containing equal parts of *A. flavus*, *A. fumigatus*, *A. glaucus*, *A. nidulans*, *A. niger*.

*Penicillium mixture*—containing equal parts of *P. camemberti*, *P. chrysogenum*, *P. digitatum*, *P. notatum*, *P. roqueforti*.

*Trichophyton mixture*—containing equal parts of *T. gypsum*, *T. interdigitale*, and *Epidermophyton inguinale*.

Fungus Allergens-Arlington are made according to a standard method, viz., grown in a peptone-cerulose-yeast extract media, collected by filtration, washed with acetone, and ether and dried.

Fungus Allergen Extracts-Arlington are prepared as follows: (directions for preparation of 1000 cc. of extract 1:20 concentration).

Fifty grams of dried fungus material are suspended in 800 cc. of N/20 sodium hydroxide, and the suspension is placed on the shaking machine for four hours. The suspension is centrifuged and decanted, and the residue is exhausted by successive extractions with N/20 sodium hydroxide until the total volume of the N/20 sodium hydroxide fractions equals 850 cc. Ethyl alcohol (95%) is added to the extract to yield a 14 per cent alcoholic solution, and the extract is filtered through paper pulp until clear. The reaction of the solution is adjusted to pH 8.3 by the addition of either hydrochloric acid, or sodium hydroxide. Tricresol in the proportion of 0.4 per cent is added, and the solution sterilized by filtration through a Berkefeld filter. The finished products are placed on sterility tests, and mouse test according to the methods required by the U. S. Public Health Service.

From this 1:20 extract, necessary dilutions are prepared aseptically with a diluent of sterile phosphate buffer containing 14 per cent alcohol by volume and 0.4 per cent tricresol. The intermediate and finished products are tested for sterility according to the methods required by the U. S. Public Health Service.

## Pollen Extracts

ABBOTT LABORATORIES

**Concentrated Pollen Extracts: 2 cc. and 5 cc. vials.**

U. S. patent 1,977,803 (Oct. 23, 1934; expires 1951).

*Annual Sage; Arizona Ash; Ash; Bermuda Grass; Black Walnut; Biennial Sage; Blue Grass; Box Elder Burweed Marsh Elder; Canada Blue Grass; Cocklebur; Corn; Cosmos; Costal Sagebrush; Cottonwood; Crab Grass; Dandelion; English Plantain; Elm; False Ragweed; Giant Ragweed; Goldenrod; Goose Grass; Hemp; Hickory; Johnson Grass; Lamb's Quarters; Marsh Elder; Mixed Grass (Blue Grass, Timothy, Orchard Grass, Red Top, and Sweet Vernal Grass in equal parts); Mixed Ragweed (Ambrosia elatior and Ambrosia trifida); Mountain Cedar; Mugwort; Oak Concentrated; Orchard Grass; Ox-Eye Daisy; Palmer's Amaranth; Plantain; Prairie Sage; Quailbrush; Redroot Pigweed; Red Sorrel; Redtop; Russian Thistle; Sage-brush; Short Ragweed; Slender False Ragweed; Southern Ragweed; Spiny Amaranth; Sunflower; Sweet Vernal Grass; Sycamore; Timothy; Western Ragweed; Western Water Hemp; Yellow Dock; Yellow Fox-Tail.*

Concentrated pollen extracts-Abbott are prepared by extracting dried pollen with a menstruum composed of 5 per cent of dextrose and 0.5 per cent of phenol in distilled water. The extract is clarified and sterilized by filtration. The finished liquid is a 3 per cent extract of the dried pollen, each cubic centimeter representing 0.03 Gm. of dried pollen (30,000 units).

**Pollen Extracts:** Extracts marketed in the following forms: Treatment sets of 16 vials containing for each consecutive dose

(1 to 16, inclusive) 10, 20, 40, 70, 100, 200, 400, 700, 1,000, 1,500, 2,000, 3,000, 4,000, 5,000 and 5,000 pollen units, respectively, accompanied by a vial containing three 0.025 Gm. capsules ephedrine hydrochloride.

U. S. patent 1,977,803 (Oct. 23, 1934; expires 1951).

*Mixed Grass (Timothy, June Grass, Orchard Grass, Red Top and Sweet Vernal Grass in equal proportions); Ragweed (Ambrosia elatior and Ambrosia trifida).*

Extracts marketed in special dilution sets:

*Mixed Ragweed Pollen Extract Decimal Dilution Set:* A mixture of equal parts of short and giant ragweed pollen extract, marketed in packages of four vials containing respectively, 5 cc. of a 1:10,000 dilution (100 pollen units per cubic centimeter), 5 cc. of a 1:1,000 dilution (1,000 pollen units per cubic centimeter), and two 5 cc. vials of a 1:100 dilution (10,000 pollen units per cubic centimeter).

*Mixed Grass Pollen Extract, Decimal Dilution Set:* A mixture of equal parts of June grass, timothy, orchard grass, redtop, and sweet vernal grass pollen extracts, marketed in packages of four vials containing respectively, 5 cc. of a 1:10,000 dilution (100 pollen units per cubic centimeter), 5 cc. of a 1:1,000 dilution (1,000 pollen units per cubic centimeter), and two 5 cc. vials of a 1:100 dilution (10,000 pollen units per cubic centimeter).

Pollen extracts-Abbott are prepared by extracting dried pollen with a menstruum composed of 5 per cent of dextrose and 0.5 per cent of phenol in distilled water. The extract is clarified and sterilized by filtration. The finished liquid is a 3 per cent extract of the dried pollen, each cubic centimeter representing 0.03 Gm. of dried pollen (30,000 units). Dilutions are prepared with additional menstruum.

**Pollen Extracts Diagnostic:** For skin testing the extracts are supplied in vials of 3 and 50 mg. capillary tubes, each tube providing sufficient material for one scratch test.

#### THE ARLINGTON CHEMICAL COMPANY

**Pollen Allergens:** Hyposensitization extracts of the following pollens are marketed in sets of five 3 cc. vials of graduated concentrations viz., 1:10,000; 1:5,000; 1:1,000; 1:500; and 1:100. Concentrations of 1:33 and 1:50, in addition to the above, are also available in 3, 5, and 10 cc. vials. For cutaneous testing, diagnostic solutions are available in 1 cc. vials and in single test capillary tubes; dry pollens are supplied in vials containing 50 mg.

*Alder; Ash; Bermuda Grass; Beech; Birch; Box Elder; Burning Bush; Burr Ragweed; Burroweed; Burweed Marshelder; California Mugwort; Canada Blue Grass; Carelessweed; Cedar; Cocklebur; Elm; English Plantain; Goldenrod; Goosefoot; Hickory; Indian Wormwood; Johnson Grass; June (Blue) Grass; Maple; Mesquite; Mountain Cedar; Mugwort; Mulberry; Oak; Olive; Orchard Grass; Paper Mulberry; Pecan; Pigweed; Pine; Poplar (Cottonwood); Poverty Weed; Prairie Sage; Privet; Ragweed, Short; Ragweed, Slender; Ragweed, Tall; Ragweed, Western; Red Top; Rough Marshelder; Russian Thistle; Rye Grass; Sagebrush; Shadscale; Wingscale; Spiny Amaranth; Sunflower; Sweet Vernal Grass; Sycamore; Timothy; Velvet (Mesquite) Grass; Walnut; Western June Grass; Western Waterhemp; Wild Oat Grass; Willow.*

In addition, the following pollen mixtures are available in treatment sets containing five 3 cc. vials of the same concen-



trations as indicated above for individual pollen hyposensitization sets; concentrations of 1:33, and 1:50 in addition to above are also available in 3, 5, and 10 cc. vials.

*Timothy, June (Blue) Grass, Orchard Grass and Red Top.*  
*Timothy, June (Blue) Grass, Orchard Grass, Red Top and Sweet Vernal Grass.*  
*Bermuda Grass and Johnson Grass.*  
*Timothy, June (Blue) Grass, Orchard Grass, Red Top and English Plantain.*  
*Tall and Short Ragweeds.*  
*Tall and Short Ragweeds and Cocklebur.*  
*Tall and Short Ragweeds and Goldenrod.*  
*Tall and Short Ragweeds and Burweed Marshelder.*  
*Tall, Short and Western Ragweeds.*  
*Tall, Short and Western Ragweeds, Burweed Marshelder and Cocklebur.*  
*Tall and Short Ragweeds and Sunflower.*  
*Tall and Short Ragweeds, Sunflower and Goldenrod.*  
*Tall and Short Ragweeds, Sunflower, Goldenrod and Cocklebur.*  
*Tall and Short Ragweeds and Timothy.*  
*Tall and Short Ragweeds, Goldenrod and Cocklebur.*  
*Tall and Short Ragweeds, Sunflower and Cocklebur.*  
*Tall, Short and Western Ragweeds, Sunflower, Goldenrod, Cocklebur, Burweed Marshelder and Prairie Sage.*  
*Tall and Short Ragweeds, Sunflower, Goldenrod, Cocklebur and Mugwort.*  
*Tall and Short Ragweeds, June (Blue) Grass, Orchard Grass, Timothy, Red Top and Sweet Vernal Grass.*  
*Tall and Short Ragweeds and Dust.*  
*Hickory and Pecan.*

Pollen extracts-Arlington are prepared by the following method:

Three parts of defatted pollen are extracted with 84 parts of phosphate buffer, pH 8.3, using 0.1 per cent cresol as preservative, for 24 hours. During the extraction period the suspension is kept at icebox temperature except for 2 hours during which it is mechanically shaken. Sufficient ethyl alcohol is added to the suspension to make the alcohol concentration of the final filtrate 14 per cent by volume. Extraction is then continued for another 24 hours with an additional 2 hours shaking. The mixture is filtered and to the filtrate tricresol is added to a concentration of 0.4 per cent. The pH is adjusted to about 8 and the clear solution is passed through a sterilizing filter. The sterile solution is a 1:33 pollen extract containing 30,000 pollen units per cc. From this solution, necessary dilutions are prepared aseptically with sterile phosphate buffer, containing 14 per cent alcohol by volume and 0.4 per cent tricresol, as diluent. The finished products are tested for sterility according to the methods required by the U. S. Public Health Service.

**BARRY ALLERGY LABORATORY, INC.**

**Allergenic Extracts:** The following extracts are marketed in complete treatment set packages consisting of three 5 cc. vials representing graduated concentrations, namely, 1 in 100, 1 in 1,000 and 1 in 10,000 respectively; 50 per cent glycerine plus 0.5 per cent phenol used as preservative.

*Grass Mixture (Spring), (June Grass, Timothy, Red Top, Sweet Vernal Grass and Orchard Grass, in equal proportions); Ragweed (Large and Small Ragweed, in equal proportions).*

Pollen extracts-Barry are prepared by grinding the dried pollen in a ball mill with a liquid containing 50 per cent glycerine, 0.275 per cent sodium chloride, 0.074 per cent sodium phosphate, 0.0285 per cent potassium dihydrogen phosphate and 0.5 per cent of phenol. The originally prepared solution represents a 3 per cent extract (30,000 pollen

units per cubic centimeter), which is subsequently diluted to the desired concentration. The extract is subjected to Berkefeld filtration, and is tested for sterility before dilution, after dilution and after filling, as required by the National Institute of Health. The finished liquid contains 50 per cent of glycerin and 0.4 per cent of phenol. The pollen unit corresponds to 0.001 mg. of dried pollen.

#### CUTTER LABORATORIES

**Allergenic Extracts:** The following extracts are marketed in complete treatment set packages consisting of four vials represented graduated concentrations, namely, 1 in 100,000, 1 in 10,000, 1 in 500 and 1 in  $33\frac{1}{3}$ , respectively; and in single vial packages containing 5 cc. of a 1:  $33\frac{1}{3}$  solution; 0.5 per cent phenol (phosphate buffer, pH 7.4) used as preservative.

*Acacia; Alder; Alfalfa; Alkali Rye; Alkali Weed; All Scale; Almond; Annual June Grass; Annual Saltbush; Ash; Aspen; Awnless Brome Grass; Barnyard Grass; Barley, Wall; Barley, Field; Bent Grass; Bermuda Grass; Birch; Blue Grass, Canadian; Box Elder; Brome Grass; Broncho Grass; Bract Scale; Burning Brush; Buttercup; Canary Grass; Careless Weed; Castor Bean; Cedar, Deodar; Cedar, Incense; Cedar, Mountain; Chaparral Broom; Cheat Grass; Chrysanthemum; Clover, Sweet; Cocklebur; Coreopsis; Corn; Cosmos; Cottonwood; Curly Dock; Cypress, Monterey; Dandelion; Dahlia; Date; Elm; Eucalyptus; Fescue, Meadow; Fir; Goldenrod; Greasewood; Hazelnut; Hollyhock; Hops; Johnson Grass; June Grass; Koehler's Grass; Lamb's Quarter; Lenscale; Locust; Maple; Marigold; Marsh Elder; Mesquite; Mexican Tea; Mugwort; Mustard; Oak, Coast Live; Oak, White Valley; Oaks, Field; Oat Grass, Tall; Oat Grass, Wild; Olive; Orchard Grass; Pecan; Pickleweed; Pigweed, Redroot; Pigweed, Spiny; Pigweed Tumbleweed; Pine, Lodgepole or Tamarack; Pine, Monterey; Pine, Yellow; Plantain; Poverty Weed; Privet; Pussywillow; Pyrethrum; Quack Grass; Rabbit Bush; Ragweed, False Coastal; Ragweed, Common; Ragweed, False; Ragweed, Giant; Ragweed, Slender; Ragweed, Southern; Ragweed, Western; Redscale; Red Top Grass; Redwood; Rose; Rye, Perennial; Rye Cultivated; Russian Thistle; Sagebrush, Coast; Sagebrush, Common; Sagebrush, Pasture; Sagebrush, Prairie; Salt Grass; Shad Scale; Shasta Daisy; Sheep Sorrel; Spear Scale; Squirrel Tail; Sugar Beet; Sunflower; Sweet Vernal Grass; Sycamore; Timothy Grass; Tree of Heaven; Velvet Grass; Walnut, Black; Walnut, English; Western Water-hemp; Wheat, Field; Wheat Grass, Slender; Willow.*

Allergenic extracts-Cutter are prepared by extracting the dried pollen with a menstruum composed of 50 per cent of glycerin in a buffered physiologic salt solution to which 0.5 per cent phenol has been added. The buffer is prepared by mixing 100 cc. of M/3  $\text{KH}_2\text{PO}_4$  (45.4 Gm.  $\text{KH}_2\text{PO}_4$  per liter) and 900 cc. of M/3 solution  $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$  (119.0 Gm.  $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$  per liter). Two per cent of this buffer solution is used to yield a final pH (after sterilization) of 7.4.

The allergenic extract is clarified by Berkefeld filtration. The finished liquid is a 3 per cent extract of the dried pollen, each 1 cc. representing 0.03 Gm. of dried pollen. Dilutions containing the equivalent of 0.002 Gm. of pollen per cc. and dilutions containing the equivalent of 0.0001 Gm. of pollen per cc. are prepared by diluting the 3 per cent extract with the same solution as was used for extraction.

#### HOLLISTER-STIER LABORATORIES

**Pollen Extracts:** The following extracts are marketed in treatment sets of four vials containing, respectively 10, 100, 1,000 and 10,000 pollen units per cubic centimeter, preserved with 50 per cent glycerine, and in single vials of 1, 2, 5, 10 and 20 cc. quantities.

For diagnostic purposes these pollen extracts are marketed in regional sets containing 0.5 cc. of each extract, sufficient for

eight or ten tests; and in single vials of 1 cc. The vials are fitted with rubber bulbs and glass droppers.

*Acacia; Alder; Alfalfa; Ash (White); Aspen; Atriplex; Awnless Brome Grass; Beech; Bermuda Grass; Blue Bunch Grass; Box Elder; Canada Blue Grass; Careless Weed; Cedar (Mountain); Cheat; Clover; Cocklebur; Corn; Cottonwood (Common); Crested Koeleria; Dandelion; Dock (Yellow); Eastern Ragweed; Elm; English Plantain; Fescue (Meadow); Giant Poverty Weed; Goldenrod; Johnson Grass; Kentucky Blue Grass; Kochia; Lamb's Quarters; Maple (Hard); Mugwort; Oak (White); Olive; Orchard Grass; Perennial Rye Grass; Pine (Yellow); Quack Grass; Redroot Pigweed; Redtop; Russian Thistle; Sage (Common); Sage (Pasture); Sage (Prairie); Sagebrush (Common); Sanberg's June Grass; Sheep Sorrel; Short Ragweed; Spear Scale; Spring Birch; Sugar Beet; Sweet Vernal Grass; Sycamore; Timothy; Velvet Grass; Walnut (English); Western Ragweed; Western Water Hemp; Wheat (Cultivated); Willow and Wormwood.*

Pollen extracts-Hollister-Stier are prepared by extracting the dried pollen with a menstruum composed of 50 per cent of glycerine, 5 per cent of sodium chloride and 45 per cent distilled water. The extract is clarified by Seitz filtration. The finished liquid is a 5 per cent extract of the dried pollen each cubic centimeter representing 50,000 pollen units, 1 unit corresponding to 0.001 mg. of dried pollen.

#### NATIONAL DRUG COMPANY

**Allergenic Extracts:** The following pollen extract is marketed in packages of three 5 cc. vials representing, respectively, 2,500, 5,000, and 10,000 nitrogen units per cubic centimeter; and in single 5 cc. vial packages of 10,000 and 25,000 nitrogen units per cc. for maintenance dosage. Each package is accompanied by a 1 cc. vial, 150 units per cc. concentration, for preliminary dosage or determination of degree of sensitivity.

For determining patient hypersensitivity by means of the scratch test the extracts are supplied in individual capillary tubes containing sufficient material for one test.

The following preparations are marketed in 10 cc. and 15 cc. vial packages representing, respectively, 2,500, 5,000, 10,000 and 25,000 nitrogen units per cubic centimeter:

*Ragweed (Giant and Dwarf Ragweed in equal parts), Mixed Grass (Timothy, 75 per cent; June Grass, Orchard Grass, Red Top, Rye, and Sweet Vernal Grass, each 5 per cent).*

Allergenic extracts are prepared by the following method: The pollen is weighed and extracted with ether. After removal of the ether the material is mixed with the extracting liquid consisting of a 0.5 per cent sodium chloride solution containing approximately 0.28 per cent of sodium bicarbonate and 0.4 per cent of phenol and then covered with toluene. After four days, during which time the mixture is shaken once or twice daily, the supernatant fluid is decanted and the sediment mixed with a second portion of extracting fluid. As soon as the sediment has settled, the supernatant fluid is decanted and mixed with the first portion. The combined decanted fluid is then subjected to Berkefeld filtration and tested for sterility. The nitrogen content of the extract is determined and dilutions are prepared on a basis of 0.00001 mg. of nitrogen per unit.

#### PITMAN-MOORE CO., DIVISION OF ALLIED LABORATORIES, INC.

**Allergenic Extracts:** The following pollen extracts are marketed in single 5 cc. vials containing 10,000 units per cubic centimeter and in packages containing one 5 cc. vial of the extract, together with three vials containing 4.5 cc. of sterile

isotonic sodium chloride diluent for the preparation of solutions containing 1,000, 100 and 10 pollen units per cubic centimeter.

*Mixed Grass (Sweet Vernal Grass, Blue Grass, Johnson Grass, Redtop and Timothy, in equal parts); Ragweed Pollens (Mixed) (Giant Ragweed and Short Ragweed, in equal parts).*

Allergenic extracts-Pitman-Moore are prepared by the following method: The dried pollens are extracted with a menstruum containing an equal volume of glycerin and water, to each hundred cubic centimeters of which has been added sodium chloride 0.15 Gm., sodium bicarbonate 0.135 Gm. and sodium ethylmercuri thiosalicylate 10 mg. as a preservative. After extraction for seventy-two hours the mixture is filtered through paper and then through a Berkefeld filter. The extract is tested for sterility after filtration and also after filling. The finished product represents a 1 per cent extract of the dried pollen. Each cubic centimeter represents 10,000 pollen units; 1 unit corresponds to 0.001 mg. of dried pollen.

#### U. S. STANDARD PRODUCTS COMPANY

**Allergenic Extracts:** The following pollen extracts are supplied in 5 cc. vials containing 20,000 units per cubic centimeter. In addition, two of the products (Grasses Combined and Ragweed Combined) are marketed in single treatment set packages of three vials, containing respectively 100, 1,000 and 10,000 units per cubic centimeter and accompanied by a vial containing 2 cc. of epinephrine hydrochloride solution 1:1,000. Five tenths per cent of phenol is used as preservative.

For the diagnostic scratch test highly concentrated pollen extract solutions are supplied in individual capillary tubes containing sufficient material for one test.

*Alder (Tag); Alfalfa; Bermuda Grass; Birch (Black); Birch (White); Box Elder; Burning Bush; Burweed; Careless Weed; Cedar (Mountain); Chrysanthemum; Clover (Red); Clover (Sweet); Cocklebur; Corn; Cosmos; Cottonwood (Poplar); Dahlia; Daisy (Ox-Eye); Dandelion; Elm; English Plantain; Goldenrod; Grasses Combined (Bermuda Grass, June Grass, Orchard Grass, Red Top, Sweet Vernal Grass and Timothy in equal parts); Johnson Grass; June Grass; Lamb's Quarters; Maple; Marsh Elder; Mugwort (Wormwood); Orchard Grass; Pecan; Pigweed (Red-root); Pine (White); Plantain (Narrow); Poplar (Lombardy); Ragweed (Common); Ragweed (False); Ragweed (Giant); Ragweed (Southern); Ragweed (Western); Ragweed Combined (Giant and Common Ragweed in equal parts); Red Oak; Red Top; Russian Thistle; Rye Grass; Sage (Common); Sage (Prairie); Sheep Sorrel; Sudan Grass; Sunflower; Sweet Vernal Grass; Sycamore; Timothy; Velvet Grass; Walnut (Black); Water Hemp (Western); Wheat (Field); White Ash; White Oak; Yellow Dock.*

The following product is supplied in 5 cc. vials representing 30,000 pollen units per cubic centimeter and in packages of four 5 cc. vials representing, respectively, 100, 1,000, 10,000 and 10,000 pollen units per cubic centimeter:

*Ragweed Combined (Giant and Common Ragweed in equal parts).*

The following product is supplied in 5 cc. vials representing 30,000 pollen units per cubic centimeter:

*Grasses Combined (Bermuda, June Grass, Orchard Grass, Red Top, Sweet Vernal Grass and Timothy in equal parts).*

Prepared by extracting the dried pollen with a menstruum containing 67 per cent glycerin and 33 per cent of a physiologic solution of sodium chloride containing 0.0908 per cent monopotassium phosphate and 0.238 per cent monosodium phosphate. The pollen is extracted for twenty-two hours in a ball mill, pulped and clarified by Berkefeld filtration. The finished liquid is a 3 per cent extract of dried pollen. Each cubic centimeter represents 30,000 pollen units, one pollen unit being the equivalent of 0.001 mg. of dried pollen. The marketed products represent approximate dilution of this stock solution and are preserved with 0.5 per cent of phenol.

#### WYETH, INCORPORATED

**Allergenic Extract:** The following extract is marketed in treatment packages of five 1 cc. size cartridge ("Tubex") vials representing graduated concentrations, namely 100, 1,000, 6,000, 20,000 and 20,000 pollen units per cubic centimeter. Also in treatment packages of five 1 cc. size cartridge ("Tubex") vials, each representing 20,000 pollen units per cubic centimeter.

#### *Ragweed Combined (Giant and Short Ragweeds, in equal proportions).*

The pollen is weighed and extracted with ether. After removal of the ether the material is mixed with the extracting liquid, consisting of a 0.5 per cent sodium chloride solution containing approximately 0.28 per cent of sodium bicarbonate and 0.5 per cent of phenol and covered with toluene. After three days the extract is subjected to Berkefeld filtration and an equal quantity of sterile glycerin is added. The mixture is then tested for sterility. Standardization is on the basis of pollen units, 1 pollen unit being equivalent to 0.001 mg. of pure pollen.

### Rhus Extracts

*Rhus toxicodendron*, *Rhus diversiloba* and *Rhus venenata* are commonly known as poison ivy, poison oak and poison sumach. The first two are probably the same plant grown under different climatic conditions, but poison sumach is a distinct species. The sap of all three contains urushiol (a dihydroxy benzene with an aliphatic side chain of varying degrees of saturation) which will sensitize most people contacting the broken leaves or twigs. The lacquers obtained from rhus trees of southeastern Asia contain either urushiol or almost identical substances.

Extracts of the leaves and twigs of these plants have been employed orally and intramuscularly for the prevention and the treatment of ivy dermatitis. The literature regarding the results obtained by these therapies is confusing. It is established that a majority of sensitive people can be rendered resistant temporarily to contact with ivy by the oral administration of concentrated ether extracts of the fresh leaves and twigs. The doses required are large and recent authors conclude the large doses required are dangerous and the immunity so brief that this procedure is impractical. Recent statistical evidence shows that small oral doses neither reverse the skin sensitivity to patch test or render the patients clinically immune. Considerable statistical evidence has accumulated indicating that the subcutaneous injection of several doses of extract of increasing strength renders many susceptible people immune to casual contact. Although this evidence is not entirely satisfactory, it

is believed that at present this is the method of choice. The extracts should not be used for treatment of the acute dermatitis.

Extracts of poison ivy, oak or sumach will be considered by the Council for prophylaxis but not for the treatment of ivy, oak, or sumach dermatitis. The fresh leaves and twigs should be extracted in absolute alcohol, acetone or ether. Before extraction, these leaves and twigs should first be macerated and thoroughly dried in vacuo from the frozen state. This procedure previous to extraction prevents subsequent deterioration and precipitation of the urushiol. The extract should be standardized biologically by determining the weakest dilution of the extract which will cause reactions by patch test in approximately half of an adequate sample of the average adult population. References to subsequent dilutions and dosages of an extract based on such a standard solution can be obtained from the literature (Status of Poison Ivy Extracts, J.A.M.A. Apr. 7, 1945, p. 912). The preparations supplied by the manufacturer should allow the practitioner some latitude in dosages so certain doses may be reduced or repeated if a patient cannot tolerate the schedule of doses recommended by the manufacturer.

It is often advisable to reduce the prophylactic dose in children and very sensitive individuals. Preparations of urushiol, either natural or synthetic, should comply with the above recommendations until the dosages are established on a weight basis by future experimentation. Extracts of poison ivy, poison oak, or poison sumach may be used interchangeably for the prophylaxis of the dermatitis caused by contact with any one of these plants.

**POISON IVY EXTRACT.**—A solution of a resin extracted from the fresh leaves of *Rhus toxicodendron*.

*Actions and Uses.*—Poison ivy extract is used for prevention of the symptoms of the dermatitis produced through contact with *Rhus toxicodendron*.

*Dosage.*—For prophylaxis, two injections of 1.0 cc. each may be given two weeks apart.

#### ABBOTT LABORATORIES

**Poison Ivy Extract:** Packages of two 1 cc. ampuls. Each cubic centimeter contains 4.5 mg. of desiccated oily resin in a mixture of sweet almond and peanut oils.

Fresh leaves of *Rhus toxicodendron* are extracted with methanol. The solvent is removed in vacuo. The residue is dissolved in isopentane and decolorized by agitation with magnesium trisilicate. The solvent is removed in vacuo, and the residue is dissolved in a sterile mixture of sweet almond and peanut oils containing chlorobutanol, so that the finished solution contains 4.5 mg. of the residue per cubic centimeter and 0.5 per cent W/V chlorobutanol.

#### HOLLISTER-STIER LABORATORIES

**Poison Ivy Extract:** Packages of five rubber-stoppered vials, each containing 0.2 cc. of alcoholic extract in graduated strengths

with five vials of sterile salt solution for dilution immediately before administration.

Ten Gm. of mature leaves of *Rhus toxicodendron* are dried, pulverized and extracted 72 hours in 100 cc. of absolute ethyl alcohol. The extract is decolorized, sterilized by filtration and diluted to proper strength.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Poison Ivy Extract in Almond Oil:** 1 cc. vials.

Freshly gathered mature leaves of *Rhus toxicodendron* are macerated with acetone. The resulting extract is decolorized and dehydrated and then concentrated until the content of solid matter becomes 13 per cent. Five parts of this liquid are added to 95 parts of sterile almond oil containing 0.5 per cent of chlorobutanol and this solution is filtered.

MULFORD COLLOID LABORATORIES

**Rhus Tox Antigen:** Packages of four 1 cc. ampul vials. Each 1 cc. contains 7.5 mg. of substance dissolved in 35 per cent alcohol.

Freshly gathered leaves of *Rhus toxicodendron* are extracted with ethyl alcohol; the alcohol is removed, the residue is extracted with chloroform to remove the chlorophyll, and then treated with zinc sulfate; sodium phosphate is then added to precipitate the zinc as zinc phosphate; the precipitate is then collected and dried. The precipitate is extracted successively with ether, amyl alcohol and isopropyl alcohol in an extraction apparatus, the extractions evaporated and the residual extract dried at a low temperature.

PARKE, DAVIS & COMPANY

**Poison Ivy Extract:** 1 cc. ampuls. A 15 per cent solution of poison ivy extract, *Rhus toxicodendron* (poison ivy—poison oak) antigen in almond oil.

The dried leaves of poison ivy (*Rhus toxicodendron*) are extracted with toluene. The resulting extract is dehydrated and decolorized and then concentrated to a solid. The residue is dissolved in sterile almond oil containing 0.5 per cent chloretone as a preservative. Sufficient oil is used to make a 15 per cent extract.

PITMAN-MOORE CO., DIVISION OF ALLIED LABORATORIES, INC.

**Poison Ivy Extract with Sterile Diluent:** 1 cc. vial, marketed in a package also containing three 0.9 cc. vials of sterile diluent consisting of a sterile isotonic salt solution containing procaine hydrochloride 0.5 per cent and chlorobutanol 0.4 per cent.

Fresh leaves of *Rhus toxicodendron*, dried at temperatures not exceeding 60 C. and sieved to remove stems and leaf midribs, are macerated with absolute ethyl alcohol, using 20 cc. of alcohol for each gram of dried leaves. The extract is filtered through paper, then diluted to five times its original volume by adding absolute ethyl alcohol.

**POISON OAK EXTRACT.**—A solution of a resin extracted from the fresh leaves of *Rhus diversiloba*.

**Actions and Uses.**—Poison oak extract is used for the prevention of the symptoms of the dermatitis produced through contact with *Rhus diversiloba*.

**Dosage.**—For prophylaxis, two injections of 1 cc. each may be made, separated by an interval of two weeks.

#### HOLLISTER-STIER LABORATORIES

**Poison Oak Extract:** Packages of five rubber-stoppered vials, each containing 0.2 cc. of alcoholic extract, in graduated strengths with five vials of sterile salt solution for dilution immediately before administration.

Ten Gm. of mature leaves of *Rhus diversiloba* are dried, pulverized and extracted 72 hours in 100 cc. of absolute ethyl alcohol. The extract is decolorized, sterilized by filtration and diluted to proper strength.

#### LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Poison Oak Extract in Almond Oil:** 1 cc. vials.

Freshly gathered mature leaves of *Rhus diversiloba* are macerated with acetone. The resulting extract is decolorized and dehydrated and then concentrated until the content of solid matter becomes 13 per cent. Five parts of this liquid are added to 95 parts of sterile almond oil containing 0.5 per cent of chlorobutanol and this solution is filtered.

#### PITMAN-MOORE CO., DIVISION OF ALLIED LABORATORIES, INC.

**Poison Oak Extract with Sterile Diluent:** 1 cc. vial, marketed in a package also containing three 0.9 cc. vials of sterile diluent consisting of a sterile isotonic salt solution containing procaine hydrochloride 0.5 per cent and chlorobutanol 0.4 per cent.

Fresh leaves of *Rhus diversiloba*, dried at temperatures not exceeding 60 C. and sieved to remove stems and leaf midribs, are macerated with absolute ethyl alcohol, using 20 cc. of alcohol for each gram of dried leaves. The extract is filtered through paper, then diluted to five times its original volume by adding absolute ethyl alcohol.

**POISON SUMACH EXTRACT.**—A solution of a resin extracted from the fresh leaves of *Rhus venenata*.

**Actions and Uses.**—Poison sumach extract is used for the prevention of the symptoms of the dermatitis produced through contact with *Rhus venenata*.

**Dosage.**—For prophylaxis, two injections of 1 cc. each may be given, separated by an interval of two weeks.

#### MULFORD COLLOID LABORATORIES

**Rhus Venenata Antigen:** Packages of four 1 cc. ampul vials. Each cc. contains 7.5 mg. of substance dissolved in 35 per cent alcohol.

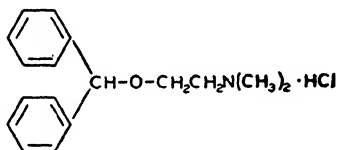
Freshly gathered leaves of *Rhus venenata* are extracted with ethyl alcohol; the alcohol is removed, the residue is extracted with chloroform to remove the chlorophyll and then treated with zinc sulfate; sodium phosphate is then added to precipitate the zinc as zinc phosphate; the precipitate is then collected and dried. The precipitate is extracted successively with ether, amyl alcohol and isobutyl alcohol in an extraction apparatus, the extractions evaporated and the residual extract dried at a low temperature.



### Histamine Antagonists

The fact that histamine has been demonstrated to have an important though partial role in allergenic reactions has led to the development of compounds that oppose it. Certain ether and ethylene-diamine derivatives possess such activity, but some are too toxic in adequate doses to have practical therapeutic application. Search for a suitable histamine-antagonizing agent has resulted in the development of relatively non-toxic compounds that are useful in the symptomatic amelioration of certain allergenic phenomena. These compounds must, however, be regarded primarily as adjuncts, and should not replace fundamental specific methods used in the treatment of allergic conditions. Their promiscuous use may be fraught with toxic reactions as yet unknown.

**DIPHENHYDRAMINE HYDROCHLORIDE.**—**Bendryl Hydrochloride** - Parke, Davis. — Beta-dimethylaminoethylbenzohydril ether hydrochloride.—The hydrochloride of diphenylmethyl ether of  $\beta$ -dimethylaminoethanol.—Diphenhydramine hydrochloride has the following structural formula:



For tests and standards, see Section B.

**Actions and Uses.**—Diphenhydramine Hydrochloride has the capacity to antagonize many of the pharmacologic effects of histamine. The drug reduces the degree of bronchoconstriction induced by histamine in guinea pigs and also in sensitized guinea pigs subjected to anaphylactic shock by the injection of antigen. In the anesthetized dog, diphenhydramine hydrochloride partially suppresses the vasodepressor action of small intravenous doses of histamine. Diphenhydramine hydrochloride possesses some musculotropic and neurotropic action, since it is reported to antagonize barium chloride and acetylcholine-induced contractions of gastro-intestinal musculature.

Diphenhydramine Hydrochloride is useful in the symptomatic treatment of urticaria, angioneurotic edema, seasonal allergic rhinitis, serum reactions, and similar allergic states. It is only occasionally of benefit in asthma and non-seasonal allergic rhinitis. It may sometimes relieve the itching of infantile eczema. Diphenhydramine Hydrochloride has been reported to have antispasmodic actions and has been recommended in pylorospasm, spastic colitis and dysmenorrhea. In general, results in these conditions have not been consistent or wholly satisfactory. More

clinical experience will be necessary before the drug can be recommended as a useful antispasmodic.

The principal side reaction noted as a result of Diphenhydramine Hydrochloride medication is somnolence. This reaction may occur in 30 or 40 per cent of those receiving therapeutic dosage and may be sufficiently pronounced to warrant discontinuance of the drug. It is important to observe caution in administering sedatives or hypnotics to patients receiving Diphenhydramine Hydrochloride. Other less frequent toxic reactions include nervousness and insomnia, nausea and other mild gastro-intestinal symptoms, occasional vomiting, numbness of the lips and tongue, vertigo and fatigue.

*Dosage.*—The smallest dose which will control the symptoms should be used. The average adult dose is 50 mgms. three or four times daily. If symptoms are controlled, the dosage should be reduced to 50 mgms. twice daily or 25 mgms. four times daily. If symptoms are not controlled, and in the absence of side effects, the dosage may be increased to 100 or 150 mgm. four times daily.

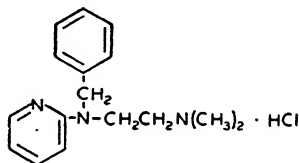
PARKE, DAVIS & COMPANY

**Kapseals Benadryl Hydrochloride:** 50 mg.

**Elixir Benadryl Hydrochloride:** 473 cc. Each 100 cc. contains Benadryl Hydrochloride 0.25 Gm., in an elixir containing alcohol, glycerin and water, with sugar, flavoring oils and added color. Each 4 cc. contains 10 mg. of Benadryl Hydrochloride.

U. S. trademark 416,252.

**TRIPLENNAMINE HYDROCHLORIDE.**—Pyri-benzamine Hydrochloride-Ciba.—N,N-dimethyl-N'-benzyl-N'-( $\alpha$ -pyridyl) ethylenediamine hydrochloride.—Beta-dimethyl-aminoethyl-2-pyridyl-benzyl ammonium chloride.—The structural formula of tripeleppamine hydrochloride may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Tripeleppamine has the capacity to antagonize many of the pharmacologic effects of histamine. It prevents histamine-induced spasm of smooth muscle and it protects guinea pigs exposed to inhalation of nebulized histamine. Tripeleppamine provides adequate protection to guinea pigs injected intravenously with lethal doses of histamine. If administered prophylac-

tically to sensitized guinea pigs, it prevents anaphylaxis to subsequent injections of antigen.

Tripelennamine has been found useful in the treatment of urticaria or seasonal allergic rhinitis and appears to be useful in treating about half of those patients suffering from non-seasonal allergic rhinitis and bronchial asthma. It may also be useful in other allergic disorders, but greater clinical experience is necessary before its precise role in the treatment of these conditions can be determined.

Tripelennamine does not affect the underlying allergic state, and therefore cessation of medication while the patient is still exposed to the allergen usually results in a prompt return of symptoms.

Approximately 30 per cent of patients experience side effects of varying degrees of severity following medication with tripelennamine. The most frequent side effect is that of drowsiness. It is important, therefore, to observe caution in administering sedatives or hypnotics to persons under treatment with this drug. Other reactions which have been observed are nausea, headache, dizziness, dryness of the mouth, nervousness and occasionally abdominal discomfort.

*Dosage.*—The smallest dose which will control the symptoms should be used. Treatment may be started with 50 mg. by mouth four times daily, preferably after meals. If symptoms are controlled, the dosage is reduced to 50 mg. twice daily or 25 mg. four times daily. Lower doses may be adequate. If symptoms are not controlled, and in the absence of side effects, the dosage may be increased to 100 or 150 mg. four times daily.

**CIBA PHARMACEUTICAL PRODUCTS, INC.**

**Tablets Pyrribenzamine Hydrochloride: 50 mg.**

U. S. patent 2,406,594.

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## CHAPTER II

# Analgesics

Analgesics are drugs used to relieve pain without producing loss of consciousness. The more potent of these are represented by morphine, its derivatives, and newer synthetic agents like merperidine, which have a central analgesic effect but present the problem of addiction. Some drugs of this general class were first used as antipyretics, and are sometimes described as antipyretic analgesics, such as salicylates, cinchophen derivatives, para-aminophenol derivatives (acetanilid and acetophenetidin), and pyrazolon derivatives (antipyrine and aminopyrine). With the advent of more effective drugs for the treatment of specific infections, the use of antipyretics as such has become less important. They may be detrimental if used against a fever without knowledge of its cause.

Quinine, the oldest of the antipyretics, is now used primarily as an antimalarial, and will therefore be described with its derivatives in the chapter on Systemic Anti-Infectives. Agents employed chiefly for general anesthesia that may be used as analgesics are described in the chapter on Anesthetics.

### Opium Principles and Derivatives

Morphine is a complex derivative of phenanthrene. It contains two OH groups (one phenolic, the other alcoholic) in which the hydrogen can be substituted by either alkyl or acid radicals.

The more important alkyl esters are the monomethyl (codeine); the dimethyl (thebaine), and ethyl-morphine. Heroin is the diacetyl derivative.

The nature of these radicals—whether acid or alcoholic, aromatic or aliphatic—modifies the actions, but only quantitatively. Replacement of one hydroxyl group (codeine) diminishes the narcotic action and increases the respiratory and tetanic action. When both OH groups are replaced by acids (diacetyl morphine), the narcotic effects are stronger than with codeine, and the tetanic action is weaker than with morphine.

*Actions and Uses.*—The central actions of all these morphine derivatives are qualitatively identical; but they present quantitative differences which have some practical importance:

*Morphine* produces the strongest analgesic, hypnotic and intestinal effects, and the weakest stimulation of the opium alkaloids. It causes the greatest derangement of digestion. It and diacetyl morphine are most liable to induce a habit.

*Codeine* (methyl-morphine) is less narcotic, less constipating and less apt to induce tolerance and habit. It is, therefore,



to occur less frequently than with morphine, the prolonged administration of dihydromorphinone should be undertaken with as much caution as would be exercised with morphine itself. Dihydromorphinone hydrochloride comes within the scope of the federal narcotic regulations.

*Dosage.*—As a sedative and for the relief of pain, the usual oral dose is 2.5 mg.; in mild pain or cough, 1.3 mg. may be given orally. The customary hypodermic dose is 2 mg. Clinically, the dose necessary to produce analgesia is about one-fifth that of morphine.

BILHUBER-KNOLL CORP.

**Solution Dilaudid Hydrochloride:** 2 mg. per cc., 1.1 cc. ampuls. Each cubic centimeter contains dihydromorphinone hydrochloride, 2 mg. in isotonic solution of sodium chloride.

**Tablets Dilaudid Hydrochloride:** 2.5 mg.

**Compounding Tablets Dilaudid Hydrochloride:** 32 mg. These tablets, each many times the average dose, are for use in compounding only.

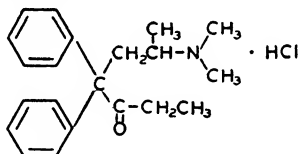
**Hypodermic Tablets Dilaudid Hydrochloride:** 1 mg., 1.3 mg., 2 mg., 3.2 mg. and 4 mg.

**Rectal Suppositories Dilaudid Hydrochloride:** 2.5 mg. dihydromorphinone hydrochloride in cacao butter base.

U. S. trademark 298,197.

## Nonopiate, Addicting Analgesics

**METHADONE HYDROCHLORIDE.** — 6-Dimethylamino-4,4-diphenyl heptanone-3-hydrochloride.—The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Methadone hydrochloride possesses, in general, a pharmacologic action similar to that of morphine. It is claimed that methadone causes less nausea and emesis, except when given orally, and less respiratory depression than morphine, with minimal analgesic doses. As a pre-anesthetic agent methadone is inferior to morphine since it is not a sedative.

Methadone hydrochloride has definite addiction liability. After its prolonged administration withdrawal symptoms have appeared, but they come on more slowly, reach their peak more slowly, and their peak intensity is less than after similar ad-

ministration of morphine. Methadone can be substituted for morphine to prevent or alleviate morphine withdrawal symptoms.

Methadone hydrochloride may be used as an analgesic agent for the relief of moderate to severe pain. It is not recommended for conditions in which the sedative effects of morphine and related drugs are of importance. The drug has a satisfactory antitussive action.

*Dosage.*—Adults, 2.5 to 10 mg. depending on the intensity and etiology of the pain. The usual dose is 7.5 mg. orally every three to four hours. For nonproductive cough, 1.25 to 2.5 mg. orally every three hours will usually be satisfactory.

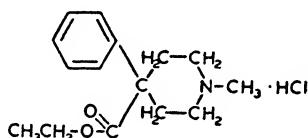
Intramuscular injection is undesirable, but subcutaneous administration in doses of 2.5 to 10 mg. will usually be effective.

#### ABBOTT LABORATORIES

**Solution Methadone Hydrochloride:** 10 mg. per cc., 1 cc. ampuls. Each cubic centimeter contains 10 mg. of methadone hydrochloride in isotonic solution with sodium chloride.

**Tablets Methadone Hydrochloride:** 2.5 mg., 5 mg. and 7.5 mg.

**MEPERIDINE HYDROCHLORIDE.**—Demerol Hydrochloride-Winthrop-Stearns. — Isonipecaine. — Ethyl-1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride. The structural formula may be represented as follows:



The base ethylmethylphenylpiperidine carboxylate may be obtained by combining dichlorodiethylmethylamine with benzylcyanide and subsequent esterification; this is converted to the hydrochloride.

For tests and standards, see Section B.

*Actions and Uses.*—Meperidine hydrochloride possesses a minor atropine effect and predominant morphine-like analgesic properties. It is capable of depressing the cardiac vagus of the anesthetized animal to the point where faradic stimulation fails to elicit any cardiac effect. Such responses are reversible.

The spasmolytic action of meperidine hydrochloride is due in part to depression of the parasympathetic endings but is primarily the result of a direct papaverine-like depression of the muscle fiber.

Therapeutic doses produce a slight sedative and a decided analgesic action. Unlike morphine, meperidine hydrochloride is not a potent hypnotic. In man the analgesic effect of merperidine hydrochloride appears to lie between that of morphine and codeine and persists for from five to six hours.

Although it has not been possible to demonstrate the development of physiologic dependence to meperidine hydrochloride in animals, the drug does possess a moderate degree of addiction liability as evidenced by the mild withdrawal symptoms observed in susceptible individuals. The development of tolerance to the drug has been demonstrated in man, and it has been shown that meperidine hydrochloride may be substituted for morphine in addicted individuals with prevention of the morphine withdrawal syndrome.

The possibility of development of psychic dependence to meperidine hydrochloride must also be kept in mind, since the drug will produce a euphoria in some individuals which lasts for an hour or more, depending on the dose.

Meperidine hydrochloride is indicated for the alleviation of pain, particularly pain of spastic origin, and in the majority of conditions in which morphine or other opium alkaloids are generally employed. In obstetrics it may be used to lessen the severity of labor pains and, in conjunction with barbiturates, to produce obstetric amnesia.

*Dosage.*—For most medical and surgical conditions the average adult dose of meperidine hydrochloride is 0.1 Gm., administered either intramuscularly or orally. In some patients pain is controlled by as little as 50 mg. Others suffering from severe pain require 0.15 Gm. For the production of analgesia in obstetrics, 0.1 Gm. is given intramuscularly as soon as contractions occur at regular intervals. If labor is rapid or if the cervix is thin and dilated (2 to 3 cm. or more) the second dose may be given as soon as one-half hour after the first one. A third dose may be necessary an hour or two later, depending on progress.

If the production of amnesia is desired, one of the barbiturates may be given when the cervix is dilated 4 or 5 cm. or when the third dose of meperidine hydrochloride is administered. In the majority of cases this procedure will insure adequate amnesia for from four to six hours. When barbiturates are used with meperidine hydrochloride for this purpose they are effective in considerably smaller doses than when used alone.

WINTHROP-STEARNs, INC.

**Demerol Hydrochloride (Powder):** 15 Gm. vials.

**Solution Demerol Hydrochloride:** 50 mg. per cc., 2 cc. ampuls and 30 cc. vials.

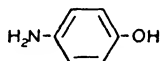


**Tablets Demerol Hydrochloride: 50 mg.**

U. S. patent 2,167,351 (July 25, 1939; expires 1956). U. S. trademark 281,130.

**Para-Aminophenol Derivatives**

*Para-aminophenol derivatives* (sometimes known as the phenetidins) are derivatives of *para*-aminophenol, whose structural

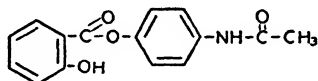


formula is given above, and are chemically related to aniline (aminobenzene). The derivatives have similar pharmacologic properties, and as they undergo decomposition in the tissues to yield either *para*-aminophenol or acetaminophenol, any difference in activity may be largely due to the rapidity with which this decomposition occurs.

Acetophenetidin and its congeners are antipyretics and analgesics and have been widely used for these effects. However, they are not without danger of untoward effects and should be used with caution. The effects produced may vary not only with the dose but with the individual patient. Undesirable reactions which have been reported following the use of antipyretics include skin eruptions, catarrh, edema of the throat and mouth, nausea and vomiting, disturbances of hearing, confusion, blood changes, heart depression and circulatory collapse. The employment of such drugs in infectious fevers should be most cautious.

Nearly every newly discovered product related to acetophenetidin has been heralded as a "safe" antipyretic and free from poisonous effects on the blood and heart. Invariably, extended clinical experience has shown that all of these preparations have, to a greater or less degree, an effect on the blood and circulation.

**PHENETSAL—Salophen-Winthrop-Stearns.**—1,4-Acetaminophenyl Salicylate.—The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions of phenetsal resemble those of phenyl salicylate (salol). It is not changed in the stomach, but is broken up in the intestine, liberating salicylic acid and *para*-aminophenol (which is less toxic than phenol). It acts as

an antirheumatic, antipyretic and analgesic. It is said to be useful in rheumatism, gout and typhoid fever. Externally, it has been applied in psoriasis and itching skin diseases.

*Dosage.*—From 0.3 to 1 Gm., in powder wafers or capsules. Externally, in 10 per cent ointment.

WINTHROP-STEARNs, INC.

**Salophen (Powder):** bulk. Phenetsal.—N. N. R.

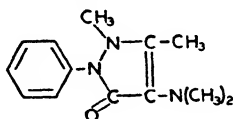
**Tablets Salophen:** 0.325 Gm.

U. S. Trademark 20,759.

## Pyrazolon Derivatives

The preparations in this group are used for their antipyretic and analgesic action and in general are subject to the same caution statements that govern the use of the phenetidin compounds. On taking small doses, some susceptible individuals experience nervous and circulatory depression, while after large doses instances of collapse have been reported. In the treatment of infectious fevers, they, as other antipyretics, should be cautiously employed. (See the general section, Para-aminophenol Derivatives.) Serious and sometimes fatal granulocytopenia may appear, especially in susceptible individuals. The drug should be immediately withdrawn if a skin eruption, dizziness, throat irritation or chill occurs; it should not be administered in large doses or over a long period of time unless repeated leukocyte and differential blood counts are made at frequent intervals. The slightest untoward symptoms are indications for withdrawal of the drug and immediate leukocyte differential count.

**AMINOPYRINE - U. S. P. — Pyramidon - Winthrop - Stearns.** — Amidopyrine. — 1-Phenyl-2,3-dimethyl-4-dimethylamino-5-pyrazolone (cf. formula below) or, more properly, 1,5-dimethyl-2-phenyl-4-dimethylamino-3-pyrazolone. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Aminopyrine and Aminopyrine Tablets and The National Formulary under Aminopyrine Elixir.

*Actions and Uses.*—Aminopyrine acts as an antipyretic and anodyne, similarly to antipyrine, but is effective in smaller doses. The action, while somewhat slower at the beginning, is more

lasting. The drug should not be used in the treatment of dysmenorrhea or for any other purpose at or near the menstrual period. Special attention is called to the dangerous side actions mentioned in the preceding article, Pyrazolon Derivatives.

*Dosage.*—From 0.3 to 0.4 Gm., most conveniently in the form of tablets, a single dose usually sufficing for twenty-four hours.

ABBOTT LABORATORIES

**Tablets Aminopyrine:** 0.325 Gm.

MERCK & Co., INC.

**Aminopyrine (Powder):** bulk.

THE WM. S. MERRELL COMPANY

**Tablets Aminopyrine:** 0.324 Gm.

WINTHROP-STEARNs, INC.

**Pyramidon (Powder):** bulk.

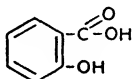
**Elixir Pyramidon:** Each 4 cc. contains Pyramidon, 0.162 Gm. in a menstruum containing alcohol 20 per cent.

**Tablets Pyramidon:** 0.13 Gm. and 0.325 Gm.

U. S. patent expired. U. S. Trademark.

### Salicylic Acid Compounds

To avoid the disagreeable taste and gastric symptoms of salicylic acid, the structural formula of which is given below,



and its salts, esters of salicylic acid have been introduced. These esters are more or less insoluble, so that the salicyl radical is liberated only in the intestine or after absorption into the blood. Esters of salicylic acid may exert direct action on the stomach; recent work suggests the possibility of gastric ulcer formation if the compounds are not properly diluted or made otherwise tolerable before ingestion. In this respect, these compounds are not superior to sodium salicylate, which does not produce direct gastric irritation when properly guarded by a bicarbonate. The taste, however, is much less objectionable than that of the simpler salicylate salts.

Compounds which hydrolyze to produce salicylic acid may be of the following types:

1. Simple salts of salicylic acid, e. g., sodium salicylate.
2. Acyl esters of salicylic acid involving the phenolic hydroxyl group, e. g., acetylsalicylic acid.

3. Alkyl and aryl esters of salicylic acid involving the carboxylic group, e. g., methyl salicylate and phenyl salicylate, respectively.

The acyl derivatives (acetylsalicylic acid type) possess a higher analgesic and antipyretic action than simple salicylate salts.

The alkyl esters (methyl salicylate type) are absorbed readily from the skin and are therefore better for external use than simpler salicylates.

The aryl esters (phenyl salicylate type) hydrolyze to active phenols and salicylic acid. They have been used for intestinal antiseptics, but are of doubtful value.

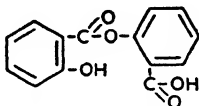
**EQUIVALENTS OF 100 PARTS OF VARIOUS SALICYLIC ACID  
DERIVATIVES IN TERMS OF SALICYLIC ACID  
AND SODIUM SALICYLATE:**

100 Parts of	Equivalent Parts of Salicylic Acid	Equivalent Parts of Sodium Salicylate
Salysal .....	106.2	124
Salicylic acid .....	100	116
Sodium salicylate .....	86	100
Acetylsalicylic acid .....	77	89
Sal-ethyl carbonate .....	77	89
Novaspirin .....	62	72

***Acid Derivatives (Acyl Esters) of Salicylic Acid***

These are employed as analgesics and antipyretics in rheumatic conditions, and in colds, neuralgias, etc. Their analgesic effects surpass those of sodium salicylate. Their acid character causes some local irritation, which may be quite marked when large doses are taken. The promiscuous use of acetylsalicylic acid (aspirin) by the laity, especially for the relief of headache, has led to rather severe poisoning, the chief symptoms being edema of the lips, tongue, eyelids, nose or of the entire face; also urticarial rashes, vertigo, nausea and sometimes cyanosis. Atopic asthmatic persons are especially susceptible to these effects of acetylsalicylic acid and several deaths have been reported from its use by such individuals.

**SALICYL SALICYLIC ACID**—Salysal - Rare.—The salicylic ester of salicylic acid.—The structural formula of this compound may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—See preceding article, Acid Derivatives of Salicylic Acid. Being insoluble in water and dilute acids,

salicyl salicylic acid is said to be relatively free from disagreeable taste and local irritating action.

*Dosage.*—From 0.3 to 0.6 Gm. two to three times a day. Salicyl salicylic acid is approximately twice as active therapeutically as sodium salicylate and may be employed in one-half the dosage of the latter drug.

RARE CHEMICALS, INC.

**Salysal (Powder):** bulk.

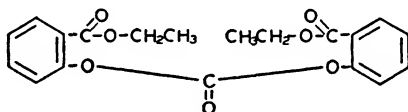
**Tablets Salysal:** 0.325 Gm.

U. S. Patent 922,995 (May 25, 1909; expired). The firm has relinquished Trademark rights to the name.

### *Alkyl Esters of Salicylic Acid*

These act somewhat more slowly, but otherwise as efficiently as sodium salicylate. They are for the most part saponified in the intestines, but some may be absorbed unchanged. They frequently cause somewhat more local irritation. They are also quite well absorbed from the skin, and may, therefore, be applied externally, usually dissolved in olive oil. Methyl salicylate is official in the U. S. Pharmacopeia.

**CARBETHYL SALICYLATE**—Sal-Ethyl Carbonate.—**Parke, Davis.**—Salicylic Ethyl Ester Carbonate.—The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Carbethyl salicylate provides the antipyretic and analgesic effects of the salicylates. It is relatively insoluble in water and in the acid secretions of the stomach practically avoiding the disagreeable taste and local gastric symptoms of the soluble salicylates. For cases requiring a rapid analgesic and antipyretic effect rather than salicylate saturation, tablets sal-ethyl carbonate with aminopyrine are supplied; but it should be recalled that aminopyrine may produce dangerous granulocytopenia in occasional individuals.

*Dosage.*—Carbethyl salicylate and tablets carbethyl salicylate with aminopyrine may be given in dosages ranging from 0.3 to 1 Gm. three or four times daily, according to the individual requirements.

PARKE, DAVIS & COMPANY

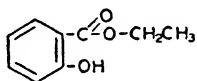
**Sal-Ethyl Carbonate (*Powder*):** bulk.

**Tablets Sal-Ethyl Carbonate:** 0.325 Gm.

**Tablets Sal-Ethyl Carbonate with Aminopyrine:** Each tablet contains Sal-Ethyl Carbonate 0.23 Gm. and aminopyrine U. S. P. 0.1 Gm.

U. S. Trademark 92,115.

**ETHYL SALICYLATE**—**Sal-Ethyl-Parke, Davis.**—The salicylic acid ester of ethyl alcohol analogous to methyl salicylate (oil of wintergreen). The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Ethyl salicylate has the same action as methyl salicylate, but is said to be less irritant and less toxic.

*Dosage.*—From 0.3 to 0.6 cc. three or four times a day.

PARKE, DAVIS & COMPANY

**Capsules Sal-Ethyl:** 0.3 cc.

U. S. Trademark 92,115.

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## CHAPTER III

# Anesthetics

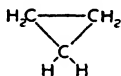
### General Anesthetics

General anesthetics are drugs which depress the central nervous system in a progressive manner. Moderate dosage of many of them reduces or abolishes the perception of pain (analgesia) before consciousness is lost. The various reflex mechanisms are likewise inhibited in an orderly progression more or less characteristic of each drug.

To be effective such drugs must enter the blood stream to be carried to the nervous system. Portals of entry are the lungs (inhalation); the gastro-intestinal tract (oral or rectal administration); or by direct intravenous injection. Certain agents may be given by any of the three routes (e.g. ether).

The physical signs by which the extent of effect of these drugs may be estimated are based largely upon the resulting changes in the sensitivity of various reflexes as the dose is increased. Thus, general anesthesia is divided into stages and planes such as are described in the textbooks. Some drugs formerly looked upon as hypnotics are now used in much larger doses as general anesthetics (e.g. barbiturates). There can be no sharp delineation between hypnotics, sedatives and general anesthetics since effects are dependent upon the size of the dose as well as upon the pharmacological characteristics of the drug. For this reason, so-called basal anesthetics are described along with the general anesthetics.

**CYCLOPROPANE-U. S. P.**—Cyclopropanum.—Trimethylene.—“Contains not less than 99 per cent by volume of  $C_3H_6$ ”—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Cyclopropane.

**Actions and Uses.**—Cyclopropane differs from other gaseous anesthetic agents in that the anesthetic-oxygen ratio is reversed—15 per cent of cyclopropane to 85 per cent of oxygen up to the rarely and briefly used 40 per cent of cyclopropane and 60 per cent oxygen. The high anesthetic potency of cyclopropane as compared with other hydrocarbons makes its use advan-

tageous from the standpoint that abundant concentrations of oxygen may be used. There is evidence to indicate that the rate of diffusion of cyclopropane is about twice that of ethylene. Cyclopropane is eliminated less rapidly than ethylene but much faster than ether. Induction and recovery with cyclopropane are therefore slower than with ethylene but more rapid than with ether.

There is some evidence to indicate that cyclopropane affects the autonomic tissue of the heart more than ether or chloroform. In high concentrations it heightens the irritability of this tissue and predisposes to the occurrence of cardiac arrhythmias. This effect has been shown to be enhanced with the simultaneous use of epinephrine. For these reasons the pulse must be carefully observed and the use of sympathomimetic drugs avoided during cyclopropane anesthesia. Cyclopropane does not stimulate respiration as do many other general anesthetic agents, and for this reason preoperative sedation with respiratory depressants must be used with caution. The signs of Guedel for other anesthetic agents do not apply to cyclopropane, so that familiarity with the signs of the stages of anesthesia for cyclopropane is absolutely essential in the administration of this agent.

The explosibility of cyclopropane-oxygen mixtures is greater than that of other anesthetic-oxygen mixtures because of the comparatively larger amounts of oxygen that are compatible with cyclopropane anesthesia. Any inert gas such as helium should be added to decrease the explosive hazard inherent with high oxygen concentrations. Careful operating room technic to avoid conditions conducive to the production of electrostatic sparks and the presence of open flames and the cautery should be observed with the same precautions as those for other explosive or inflammable anesthetics.

The advantages of cyclopropane consist in its effectiveness in concentrations providing an adequate supply of oxygen, less pulmonary irritation than ether (except in asthmatics), less excitement during induction and low toxicity. Its disadvantages include explosibility when oxygen-rich mixtures are employed, lack of respiratory stimulation, difficulty in detection of the planes of anesthesia by those unfamiliar in its administration, occasional laryngospasm, and tendency to produce cardiac arrhythmias and postanesthetic headache.

*Dosage.*—Cyclopropane is usually furnished in compressed form in metal containers. In use the gas is passed into an inhalation apparatus of the closed circuit type and is then administered by inhalation from a rebreathing bag, always with the admixture of oxygen. The concentration employed varies from 15 to 40 per cent and with the individual patient but should probably not exceed 30 per cent. The remainder of the mixture should consist of a minimum of 20 per cent oxygen, but this should be supplied in quantities adequate for physiologic needs. When other anesthetics are used in combination



or when premedication has been employed, less cyclopropane is required.

*Caution.*—Cyclopropane is inflammable and its mixture with oxygen or air may explode when brought in contact with a flame or other causes of ignition.

OHIO CHEMICAL & MFG. COMPANY

**Cyclopropane:** Cylinders.

E. R. SQUIBB & SONS

**Cyclopropane:** 151.4 liter, 378.5 liter and 757 liter cylinders.

**ETHYL CHLORIDE—U. S. P.—Kelene—Merck.**

The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Ethyl Chloride.

*Actions and Uses.*—Ethyl chloride is used for minor operations in the form of spray to produce local anesthesia by refrigeration. When inhaled it produces prompt anesthesia, suitable only for very short operations. It is useful for inducing anesthesia before the administration of ether; but even then it is not without danger similar to that from chloroform.

*Caution.*—As the vapor is very inflammable, Ethyl Chloride must not be used near flame.

MERCK & Co., INC.

**Kelene (Liquid):** Ethyl chloride. 30 Gm., 60 Gm. and 100 Gm. tubes with automatic closures.

U. S. trademark 63,705.

**ETHYLENE—U. S. P.**—"Contains not less than 99 per cent by volume of  $\text{C}_2\text{H}_4$ ."—U. S. P. The structural formula of ethylene may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Ethylene.

*Actions and Uses.*—Animal experiments by W. E. Brown (*Canad. M. A. J.*, March 1923, p. 210) and Luckhardt and Carter (*J. A. M. A.* 80:765 [March 17] 1923) indicated that ethylene has a direct action on the nervous system when certain high concentrations of ethylene and corresponding low concentrations of oxygen are used, that the motor reflexes are abolished with these concentrations and that the phenomena produced by the undiluted gas are partly asphyxial, which effect can be removed by addition of oxygen to the ethylene itself.

Trials on human subjects have confirmed the anesthetic and analgesic value of ethylene as demonstrated on animals. First to second plane surgical anesthesia is stated to be produced easily and analgesia comes on readily and apparently long before surgical anesthesia is established. Given with oxygen, it has been found more powerful than nitrous oxide. Unlike ether it causes minimal respiratory irritation and does not promote mucus secretion.

Extensive use of ethylene in a wide variety of conditions failed to show it to be more explosive than ether-oxygen, cyclopropane-oxygen or ether-nitrous oxide-oxygen under comparable precautions.

Under average conditions of ventilation ethylene, because of its rapid diffusibility, exists in explosive concentration (3.2 to 80 per cent) no further than two feet from the mask. Adequate ventilation of this area should eliminate largely the danger of explosion. No electrical devices should be employed when ethylene is used. The ordinary operating room technique guarding against the presence of open flames, cautery and sparks should be observed.

The advantages of ethylene over ether consist in the production of an equally rapid but more pleasant induction; satisfactory relaxation without cyanosis or sweating; rapid recovery and decreased or absent post-operative nausea. It is useful in older children and in the presence of cardiac, lung or kidney disease, thyrotoxicosis and diabetes.

*Dosage.*—Ethylene is supplied in compressed state in metal containers. For use the gas is passed into an inhalation apparatus and is then inhaled with admixture of oxygen. The concentration employed for surgical anesthesia is never in excess of 85 per cent ethylene with 15 per cent oxygen, though after a prolonged period of anesthesia, a deep anesthetic state may be maintained on 80 per cent or less ethylene. If the patient has been premedicated (e.g. morphine, barbiturate) less ethylene and more oxygen can be given. Anesthetic mixtures of less than 80 per cent ethylene are explosive so that when lower concentrations are employed precautions to avoid this hazard should be taken.

*Caution.*—Ethylene is inflammable and a mixture of it with oxygen or air will explode when brought in contact with a flame or other causes of ignition.

THE LIQUID CARBONIC CORPORATION

**Ethylene:** cylinders.

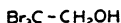
OHIO CHEMICAL & MFG. COMPANY

**Medical Ethylene Gas:** cylinders.

PURITAN COMPRESSED GAS CORPORATION

**Ethylene:** cylinders.

**TRIBROMOETHANOL SOLUTION-U. S. P.—**  
**Avertin with Amylene Hydrate-Winthrop-Stearns.**—Tribromoethyl Alcohol Solution. "A solution of tribromoethanol in amylene hydrate containing, in each 100 cc., not less than 99 Gm. and not more than 101 Gm. of  $C_2H_3Br_3O$ ." U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Tribromoethanol Solution and Tribromoethanol.

**Actions and Uses.**—Tribromoethanol Solution is used for basal anesthesia by rectal administration. It should not be employed in dosage sufficient to cause complete anesthesia. When employed for basal narcosis the amount of inhalation anesthetic necessary to establish and maintain complete anesthesia is diminished. A prolonged period of sleep usually follows termination of inhalation anesthesia; during this after-period careful nursing care and continuous vigilance are necessary to maintain an open airway and to prevent the cyanosis and respiratory failure which sometimes follow. Ephedrine, caffeine with sodium benzoate and oxygen therapy are said to be effective antidotes against respiratory and circulatory depression occurring from tribromoethanol solution.

Contraindications to the use of tribromoethanol solution (relative or absolute depending on the condition of the patient) include liver or kidney dysfunction, severe cardiac disease, hypertension, hypotension, old age, shock or dehydration, sepsis, toxemia, severe pulmonary tuberculosis, empyema, decreased vital capacity, likelihood to respiratory obstruction, marked hypothyroidism, obesity, asthenia, cachexia, ileus, pathology of the colon or rectum, enteritis and acidosis.

Tribromoethanol Solution is said to be useful in the control of certain convulsive conditions such as tetanus; in the latter condition it is used in repeated doses in conjunction with administration of tetanus antitoxin to control the seizures over a period of several days if necessary. It is useful in breaking a vicious cycle of status asthmaticus.

**Dosage.**—For each kilogram of body weight rectal, 0.06 cc. (1 minim). U. S. P.

Solution of tribromoethanol is administered rectally in 2.5 per cent solution in warm distilled water at a temperature not exceeding 40 C. A small quantity of the solution should be tested with the congo red indicator supplied with the preparation just before administration; the color of the solution should match that of an equal amount of distilled water containing an equal quantity of the congo red indicator. If the colors do not match, this indicates the presence of irritant hydrobromic acid and di-bromacetaldehyde, and the solution should be discarded.

The ordinary maximum dose for basal anesthesia is 80 mg. of tribromoethanol (40 mg. of amylene hydrate) per kilogram of

body weight. Often less will be sufficient. In young, vigorous persons the dose may sometimes be increased to 90 or 100 mg. of tribromoethanol (from 45 to 50 mg. of amylene hydrate). A dose of 30 to 50 mg. per kilogram is usually sufficient for amnesia and is not accompanied by depression of the respiration or circulation. The dose is usually stated in milligrams of the tribromoethanol component only. As the amylene hydrate adds materially to the narcotic effect, it should be kept in mind that, with each dose of tribromoethanol, half this dose by weight of amylene hydrate is administered.

The total amount administered should not exceed from 6 to 8 cc. of solution of tribromoethanol for women, or from 9 to 10 cc. for men, regardless of weight. Dosage tables are supplied by the firm.

*"Caution.—Tribromoethanol Solution should never be employed by those inexperienced in its use except under expert supervision. The total amount administered should not exceed 8 Gm. for women or 10 Gm. for men, regardless of body weight."*  
U. S. P.

WINTHROP-STEARNs, INC.

**Solution Avertin with Amylene Hydrate:** Each cc. contains tribromoethanol 1 Gm. and amylene hydrate 0.5 Gm.

U. S. patents 1,572,742 (Feb. 9, 1926; expired), 1,725,054 (Aug. 20, 1929; expired), 1,882,584 (Oct. 18, 1932; expires 1949). U. S. trademark 233,204.

**TRICHLOROETHYLENE-U. S. P.**—"Contains not less than 99 per cent and not more than 99.5 per cent of  $C_2HCl_3$ , the remainder consisting of alcohol." U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Trichloroethylene.

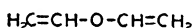
**Actions and Uses.**—The actions of trichloroethylene have not been extensively investigated. It was introduced into therapeutics as a result of observations of prolonged anesthesia of the fifth nerve following trichloroethylene exposure in industry because it was considered to have a selective action on the sensory endings of the trigeminal nerve. However, evidence is now accumulating which indicates that it is a general anesthetic rather than a specific nerve anesthetic. It must be remembered that the distribution of the fifth nerve is much greater than that of other nerves supplying the face and that trigeminal neuralgia (tic douloureux) while not a common condition, is one of the commonest of the facial neuralgias. It is, therefore, only natural that the usefulness of this agent in that particular condition should have received such prominence and that the interpretation of the results obtained seemed to indicate a special affinity which did not exist. Regardless of the fact that no

special affinity exists, trichloroethylene is a useful measure in the treatment of tic douloureux, as well as in many other painful conditions of the face.

Trichloroethylene has been proposed for use in the prevention and treatment of attacks of angina pectoris. It is believed that trichloroethylene is worthy of trial for this purpose in the clinic, provided patients are under continued medical supervision. Trichloroethylene is a general anesthetic, and its use for this purpose is subject to all the dangers and disadvantages of anesthetics. Recent studies indicate that its use as a general anesthetic is limited because it produces cardiac arrhythmia and increased muscular activity.

*Dosage.*—Trichloroethylene should never be prescribed in bulk or taken in large doses; from 1 to 3 cc. a day, in divided doses are ample. The dosage should always be taken with the patient in a reclining position, and the material should not be substituted for amyl nitrite or nitroglycerine in the treatment of the acute anginal attack. Each patient should be warned of the possibility of addiction. Excessive dosage of trichloroethylene may mask a severe attack of coronary pain, and lead to its being ignored, where it should receive immediate medical attention, together with bed rest. It should be used cautiously in the prevention of attacks because it may mask pain indicating exertion beyond the capacity of the heart.

**VINYL ETHER-U. S. P.—Vinethene-Merck.**—"Consists of about 96 per cent of  $C_4H_8O$ ,  $[CH_2:CH-O-CH:CH_2]$  and about 4 per cent of dehydrated alcohol. It may contain 0.025 per cent of a harmless preservative." U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Vinyl Ether.

*Actions and Uses.*—Vinyl ether is an inhalation anesthetic to be used for short anesthetics. It differs from ether, U. S. P., in the rapidity of its action. This property necessitates special caution in its administration. It is easy to pass from the level of surgical anesthesia to dangerous overdosage; therefore the importance of constant, close observation of the patient cannot be overemphasized. Properly watched, this rapid action is of advantage in short anesthetics, as is the prompt recovery which follows administration of the drug. The patient is completely oriented and ambulant within a few minutes. To prevent recovery from occurring before the surgical procedure is completed, vinyl ether must be administered continuously during maintenance.

The anesthetist should familiarize himself thoroughly with the properties of vinyl ether before employing it. Of major impor-

tance is the fact that the eye signs usually depended on in anesthesia are entirely unreliable. The most important single signs to follow in determining the extent of the anesthesia are the rate, depth, regularity and smoothness of respiration. If the anesthesia is administered in the proper way there should be no cyanosis and the development of such a condition is an indication for the employment of oxygen followed by the use of other anesthetic agents. Although there is occasionally an increased secretion of mucus during maintenance, even when atropine is administered, postoperative complications have not been frequently encountered. Nausea and vomiting occur in about 5 per cent of patients.

Vinyl ether is intended primarily for use in minor surgical operations of short duration, and in dentistry where gas anesthesia is not available. It is also useful as an induction anesthetic. It has been rather extensively used during labor and during postpartum obstetric procedures. It has, however, one major disadvantage when used in this branch of medicine—its rapid action has practically precluded its use for obtaining obstetric analgesia.

Under no circumstances should the anesthetic be pushed, and if proper relaxation and anesthesia are not obtained with low concentrations other agents should be employed. In case of overdosage respiration is likely to be inhibited and anoxemia and cyanosis are likely to develop. Under such circumstances the anesthetic must be discontinued, oxygen administered, and measures taken to stimulate respiration and provide an adequate airway between the lungs and the atmosphere. The explosive and fire hazards of vinyl ether are just about equal to those of ether, U. S. P.

As with most other anesthetic agents, age, cardiovascular disease, renal insufficiency or hepatic damage, particularly the latter, must be given due consideration as contraindications. It may be administered by the open drop, semiopen drop or closed machine method. It would seem at the present time that the open drop method is preferable, for the short anesthetics. In any case, an adequate oxygen or air supply is essential and an unobstructed airway is of paramount importance.

*Caution.—Vinyl ether is inflammable and deteriorates on exposure to air and light. It must be preserved in tight containers of not more than 200 cc. capacity and is not to be used if the original container has been opened longer than forty-eight hours.*

MERCK & Co., INC.

**Vinethene:** 10 cc. vials and 25, 50 and 75 cc. bottles.

U. S. patents 2,021,872 (Nov. 19, 1935; expires 1952), 2,044,800 (June 23, 1936; expires 1953), 2,044,801 (June 23, 1936; expires 1953) and 2,099,695 (Nov. 23, 1937; expires 1954). U. S. trademark 312,453.

## Local Anesthetics

Local anesthesia (that confined to a restricted area or part) may be produced in a variety of ways according to the site of application and the method or technic of administration. Topical application to mucous membranes is designated as surface anesthesia. Certain drugs (e. g., cocaine, tetracaine) are effective in this manner while others (procaine) are less satisfactory for topical application. Agents which produce freezing temperature to lower sensibility to pain (ethyl chloride, carbon dioxide snow) and protoplasmic poisons (phenol) are rarely used at present.

Local anesthesia produced by injectable compounds is designated according to the technic or anatomical site chosen: as infiltration (injection directly into the area which is painful or subjected to surgical trauma), or block (injection in proximity to specific nerve trunks supplying a particular anatomical site). Block injections are designated according to the point chosen for interruption of nerve transmission. Some of these are: *spinal* (within the dural membrane surrounding the spinal cord and nerve roots); *extra dural* or *epidural* (solutions deposited immediately outside the dural membrane, and within the bony spinal or caudal canals), and other innumerable blocks designated according to their anatomical location along the course of nerve trunks on their way to the peripheral tissues.

A special dosage form of local anesthetics may also be used to induce continuous caudal analgesia for use in obstetric cases, *provided the procedure is carried out with great care and caution and is undertaken only by skilled specialists. It is not a procedure for untrained hands.* (See caution under the general article, Local Anesthetics.) Two technics have been used: one involves the use of a special malleable needle; the other a ureteral catheter. When the special needle is used, great care must be taken to see that that portion of the needle which lies outside the skin is protected, so that movement of the patient will not force the needle up into the caudal canal or against bone or into a vein. Further the needle must be protected against breakage. The patient should not be allowed to remain in a sitting position but be instructed to lie on her side. If the needle breaks within the canal, it must be removed within a few hours. Of course such things as penetration of blood vessel and dura should be watched for constantly when the needle is being inserted.

If a ureteral catheter is to be employed, entry into the caudal canal should be made with a needle no larger than 15 gauge. If it is necessary to use a needle as large as 13 gauge and the caudal canal is not entered on the first attempt, the method should be discarded; otherwise infection is almost certain to occur. Infection is one of the great dangers encountered in continuous caudal analgesia and extreme care must be exercised to prevent this condition. There should be at hand emergency measures to control untoward reactions. Soluble barbiturates (e.g. Hexobarbital Soluble N. N. R., Thiopental Sodium

U. S. P.) are useful to control convulsions should they occur. Oxygen should be immediately accessible.

Continuous caudal analgesia is contraindicated in the presence of placenta praevia, inertia uteri, uncontrollable hysteria, anomalies of the sacrum and disproportion of child and pelvis. It is not suitable for difficult forceps rotation or version, as in such cases complete relaxation of the uterus is imperative. History of sensitivity to local anesthetics is another contraindication.

The Council has recognized the use of local anesthetics to produce caudal analgesia, so that proper warnings may be issued. It is emphasized again that this procedure should be carried out only by experienced hands and then only with great caution.

Certain local anesthetics are believed to cause vasoconstriction in the area applied (cocaine) while others do not (tetracaine). For topical application, therefore, as well as when injected, epinephrine (or similar less toxic vasoconstrictor agents e.g. neosynephrine) is usually added in the preparation of solutions to impede rapid systemic absorption. Concentration of such agents in solutions to be injected should be kept at a minimum effective level (usually from 1 part in 130,000 to 1 part in 520,000 in the case of epinephrine). (See Sympathomimetic Agents in the chapter on Autonomic Drugs.)

To combat the vasodepressor effects of the local anesthetics, especially when injected more centrally (spinal or epidural) long acting vasoconstrictor agents (e.g. ephedrine) may be injected intramuscularly or intravenously for their systemic effect.

The technical details necessary to prepare and control solutions of drugs injected, especially within the subdural or epidural spaces, are intricate and exacting. These should be acquired from authoritative source books and from instruction by experienced anesthetists. Details of dosage of any of the several local anesthetics should be learned with reference to various modifications for different applications.

The toxicity of all local anesthetic agents is great and the tolerance of patients variable. There are certain limits of strength of solution and total dosage which may not be exceeded with safety. These limits will be discussed under the drug concerned. Hence, an administration must be individualized and adjusted to the exact requirement. Choice of drug, concentration, rate and location of injection, along with age, emotional and physical status of the patient are a few of the factors involved. *One should choose the smallest amount of the least toxic drug that will serve the purpose*, if reactions are to be avoided. The use of barbituric acid derivatives as premedication is advisable to prevent or decrease toxic reactions. Accidental vascular injections are relatively frequent even in the practice of the most skillful anesthetist. Extreme caution is also imperative when any local anesthetic is applied to the traumatized urethra or under conditions in which trauma to the mucous membrane is likely to occur. Hence, when local anesthetic drugs are being used, it is in the interest of safety to have instantly available (a) oxygen and the means of inflating the lungs with it and (b) a quick act-



ing barbituric acid compound ready for intravenous administration.

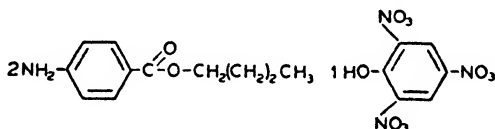
### *Slightly Soluble Local Anesthetics*

The slight solubility of these anesthetics renders them unsuitable for injection, but the slow absorption renders them safer, especially for ulcers, wounds and mucous surfaces. The anesthesia which they induce is usually not so complete as that induced by the soluble local anesthetics; but it is more lasting. As a group they are practically nonirritant and nontoxic. Ethyl aminobenzoate (benzocaine, anesthesin) and orthoform are about equally effective through intact mucous membranes; butyl aminobenzoate (butesin) is claimed to be more effective than either.

They are used for painful wounds, ulcers, etc., of the skin and accessible mucous membranes; for instance, after dental operations.

Many, if not all, local anesthetics occasionally give rise to dermatitis. When this is severe, the use of the anesthetic should be discontinued.

**BUTAMBEN PICRATE** — Butesin Picrate-Abbott. — Di-*n*-butyl-*p*-aminobenzoatetrinitrophenol.—A compound consisting of one molecule of trinitrophenol (picric acid) and two molecules of the normal butyl ester of 4-aminobenzoic acid. The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—An aqueous solution of 1 in 2,000 produces immediate and complete anesthesia of the eye which lasts from ten to twenty minutes. Butamben picrate is used in the treatment of burns, ulcers and other denuded painful lesions of the skin.

Instances of butamben picrate dermatitis have occurred which are probably due to idiosyncrasy. A development of a rash following the use of the drug is an indication for its discontinuance.

*Dosage.*—For use, a 1 per cent butamben picrate ointment is proposed.

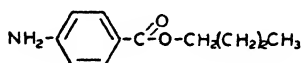
### ABBOTT LABORATORIES

**Ointment Butesin Picrate with Metaphen:** Butesin Picrate 1 per cent, and metaphen 1:5,000, incorporated in an ointment base composed of white wax, paraffin, petrolatum, sodium borate and water, 99 per cent.

**Ophthalmic Ointment Butesin Picrate 1% and Butesin 1%:** Butesin Picrate, 1 per cent; Butesin, 1 per cent and soft petrolatum, 98 per cent.

U. S. patent 1,596,259 (Aug. 17, 1926; expired). U. S. trademark 175,095.

**BUTYL AMINO BENZOATE-U. S. P.—Butesin-Abbott.**—*n*-Butyl *p*-Aminobenzoate. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Butyl Aminobenzoate.

**Actions and Uses.**—See general article, Slightly Soluble Local Anesthetics. The actions and uses of butyl aminobenzoate are similar to those of ethyl aminobenzoate-U. S. P., but it is claimed to be more effective.

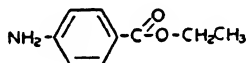
**Dosage.**—Butyl aminobenzoate is used as a dusting powder, either with or without a diluent. It may be used in the form of troches, ointment, or suppositories or dissolved in a fatty oil. Its oil solutions may be sterilized by heat.

ABBOTT LABORATORIES

**Butesin (Powder):** bulk.

U. S. patent 1,440,652 (Jan. 2, 1923; expired). U. S. trademark 175,095.

**ETHYL AMINO BENZOATE-U. S. P.—Anesthesin-Abbott.**—Anaesthesin-Winthrop-Stearns.—Benzocaine. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Ethyl Aminobenzoate and Ethyl Aminobenzoate Ointment.

**Actions and Uses.**—See general article, Slightly Soluble Local Anesthetics.

**Dosage.**—Used as a dusting powder, either with or without a diluent. It may be applied in ointment or in the form of suppositories.

ABBOTT LABORATORIES

**Anesthesin (Powder):** bulk.

U. S. trademark 55,744.

GEORGE A. BREON & Co., INC.

**Solution Benzocaine in Oil:** Bottles of 15 cc. and 480 cc. Contains benzocaine 2.5 per cent W/V and chlorobutanol 0.5 per cent W/V in cottonseed oil.

MERCK & Co., INC.

**Benzocaine (Powder):** bulk.

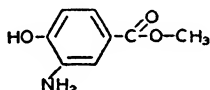
WINTHROP-STEARNs, INC.

**Anaesthesin Jelly:** 45 cc. collapsible tube.

**Anaesthesin (Powder):** bulk.

U. S. trademark 55,744.

**ORTHOFORM.** — Orthoform-New. — Methyl-*m*-amino-*p*-hydroxybenzoate.—The *m*-amino-*p*-hydroxybenzoic acid ester of methyl alcohol. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Orthoform is a local anesthetic, but penetrates the tissues very slowly on account of its insolubility. It has no action on the unbroken skin. It is practically non-toxic in the usual doses.

It has been applied locally as an analgesic to wounds of every description. It has been used in dentistry and in nasal catarrh, hay fever, etc.

**Dosage.**—The Council does not approve of the internal use of this drug. It is used as a dusting powder or mixed with milk sugar for insufflation, dissolved in ether and mixed with oil for pencillings, or as an ointment with wool fat, etc.

WINTHROP-STEARNs, INC.

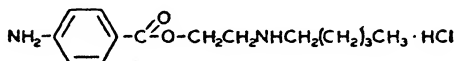
**Orthoform (Powder):** 5 Gm. vials, and 31.1 Gm. bottles.

U. S. patents 610,348 (Sept. 6, 1898; expired), and 625,158 (May 16, 1899; expired).

### *Soluble Local Anesthetics*

**AMYLSINE HYDROCHLORIDE-Novocol.**—2-*p*-Aminobenzoxy-1-*n*-amylaminoethane Hydrochloride. — (Formerly known as Amylcaine [ämyl-cäïne] Hydrochloride, the name having been changed to avoid confusion with the official preparation

of British Pharmacopeia.) The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions of amylsine hydrochloride resemble those of cocaine hydrochloride, but it does not cause mydriasis when the solution is dropped into the eye. In the present state of our knowledge its use should be restricted to the production of corneal anesthesia in those cases in which mydriasis is not desired. The toxicity varies rather widely with the species and with the mode of administration. The anesthesia is induced promptly with little smarting; it does not increase intraocular tension.

**Dosage.**—A 2 per cent or 4 per cent solution is used in ophthalmology when mydriasis is not desired, 1 or 2 drops being usually sufficient.

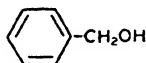
NOVOCOL CHEMICAL MFG. CO., INC.

**Amylsine Hydrochloride (Powder):** 5 Gm. vials and 30 cc. bottles.

**Solution Amylsine Hydrochloride 4%:** 30 cc. bottles.

U. S. Patent 2,139,818 (Dec. 13, 1938; expires 1955). U. S. trademark 404,009.

**BENZYL ALCOHOL-N. F.**—Phenylcarbinol.—An aromatic alcohol occurring as an ester in tolu and other balsams; the product on the market is produced synthetically. The structural formula may be represented as follows:



For description and standards see The National Formulary under Benzyl Alcohol.

**Actions and Uses.**—Benzyl alcohol is used as a local anesthetic by injection and by application to mucous membranes. It is practically nonirritant and nontoxic in the ordinary concentrations and doses. (See caution under the general article, Local Anesthetics.)

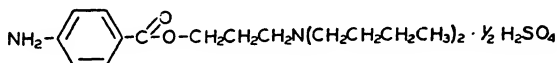
**Dosage.**—Benzyl alcohol is usually used in the form of a 1 to 4 per cent solution in water or physiological solution of sodium chloride. Such solutions may be sterilized by boiling, without danger of decomposition. Pure benzyl alcohol is markedly antiseptic. The technic of injection is the same as for other local anesthetics. It is applied against pruritus as a 10 per cent oint-

ment, in lard; or as a lotion of equal parts of benzyl alcohol, alcohol and water.

SEYDEL CHEMICAL COMPANY

**Benzyl Alcohol:** bulk.

**BUTACAINE SULFATE-U. S. P.—Butyn Sulfate-Abbott.**—3-(*p*-Aminobenzoy)-1-di-*n*-butylaminopropane Sulfate. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Butacaine Sulfate.

**Actions and Uses.**—Butacaine sulfate is a local anesthetic proposed as a substitute for cocaine, particularly in surface anesthesia, as for the eye, nose and throat. It has the special advantage of acting through intact mucosae about as effectively as cocaine. On the normal human eye, a 1 per cent solution of butacaine sulfate is as effective as a 1 per cent solution of phenacaine hydrochloride (holocaine), and more efficient than a 1 per cent solution of cocaine hydrochloride or a 1 per cent solution of eucaine. The instillation of butacaine sulfate solutions often produces congestion of the conjunctiva, but this does not appear to be of practical significance.

When butacaine sulfate is injected hypodermically into albino rats, the toxicity is two and one-half times that of cocaine, but the lethal dose (injected intravenously into cats) is about equal to that of cocaine. Pharmacologic study indicates that butacaine sulfate may take the place of cocaine, in whole or in part, for surface anesthesia of mucous membranes and that it may be superior for this purpose, especially for use in the eye, to other anesthetics, for the reason that it can be used in materially lower concentrations (presumably because of more prompt absorption). On the other hand, it does not appear promising for injection anesthesia or for spinal anesthesia, since its toxicity is materially greater than that of procaine hydrochloride; but butacaine sulfate is used for injection anesthesia, in concentrations of 0.1 to 0.4 per cent.

A committee of the Section of Ophthalmology of the American Medical Association (*J. A. M. A.* 78:343 [Feb. 4] 1922) reported the successful use of butacaine sulfate in practically all operations on the eye and in some operations on the nose and throat. The committee concluded that butacaine sulfate is more powerful than cocaine, a smaller quantity being required; that it acts more rapidly than cocaine and that the action is more prolonged. So far as the experiences of the committee go, butacaine sulfate in the quantity required is less toxic than cocaine. The committee found butacaine sulfate superior to cocaine in that it produces no drying of the tissues and no change in the size of the pupil and that it has no ischemic effect.

**Dosage.**—For ophthalmologic work, butacaine sulfate is generally used in 2 per cent solutions. A single application produces, within one minute, an anesthesia sufficient to permit the removal of superficially placed foreign bodies, the application of irritant astringents and the use of the tonometer. Four instillations, three minutes apart, permit operative work within five minutes after the last instillation, producing an anesthesia sufficient to perform all of the commoner operations on the eye. For topical use in nose and throat work, a 2 per cent solution is usually employed. Butacaine sulfate solutions may be sterilized by boiling. (See caution under the general article, Local Anesthetics.)

**ABBOTT LABORATORIES**

**Butyn Sulfate (Crystals):** bulk.

**Solution Butyn Sulfate 2% :**

**Tablets Butyn Sulfate:** 0.2 Gm.

**Hypodermic Tablets Butyn Sulfate and Epinephrine:**  
Butacaine sulfate 10 mg. epinephrine hydrochloride 0.032 mg., sodium bisulfite, 1.6 mg.

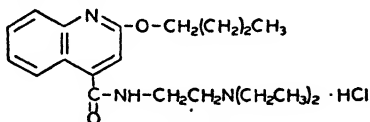
**Ophthalmic Ointment Butyn Sulfate 2% and Metaphen 1:3,000:** contains 2 per cent of butacaine sulfate with metaphen 1:3,000 in a base of petrolatum, 75 per cent and wool fat, 25 per cent.

U. S. patent 1,358,751 (Nov. 16, 1920; expired); 1,676,470 (July 10, 1928; expired). U. S. trademark 147,893.

**MANHATTAN EYE SALVE COMPANY, INC.**

**Ointment Butyn Sulfate 1% :** Butacaine sulfate, 1 per cent; water, 1 per cent; wool fat, 5 per cent, and petrolatum, sterile, 93 per cent. Put up in collapsible tubes for application to the eye.

**DIBUCAINE HYDROCHLORIDE**—Nupercaine Hydrochloride—Ciba.—2-*n*-Butoxy Diethylaminoethylamide of Quinolinecarboxylic Acid Hydrochloride.—2-Butoxy-4-( $\beta$ -diethylaminoethylamido) Carboxyquinoline Hydrochloride.—The hydrochloride of the base obtained by converting 2-hydroxyquinoline carboxylic acid to 2-chloroquinoline carboxylic acid chloride, followed by interaction of the latter with asymmetric diethylethylenediamine and subsequent heating with sodium butylate. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Dibucaine hydrochloride is a local anesthetic, acting like cocaine when applied to mucous surfaces and

like procaine or cocaine when injected, the action being relatively prolonged. Dibucaine hydrochloride is about five times as toxic as cocaine when it is injected intravenously into animals, and its anesthetic activity is correspondingly greater than that of cocaine when it is applied to a mucous surface; it is many times more active than procaine hydrochloride when it is injected subcutaneously. It is reported to have caused necrosis of tissue in one case and a condition resembling gangrene with recovery in another. Death has been reported after the subcutaneous injection of 135 cc. of a solution of 1 in 1,000. Weak solutions (1 in 2,000) cause slight temporary vascular dilatation (avoided by the addition of epinephrine hydrochloride), followed by constriction. In spinal anesthesia it should not be employed in concentrations greater than 0.066 per cent (1:1,500), nor given in amounts to exceed 20 cc. (approximately 12 mg.).

**Dosage.**—For infiltration anesthesia solutions of from 1 in 2,000 to 1 in 1,000, with the addition of 0.1 cc. of epinephrine hydrochloride solution (1 in 1,000) to 100 cc. of the solution. Not more than 100 cc. of 1 in 1,000 solution should be injected. For spinal anesthesia, a total of from 7.5 to 10 mg. in 1 in 1,500 solution which is made by diluting a 1 in 200 solution with an appropriate quantity of spinal fluid; for sacral anesthesia, 25 to 35 cc. of 1 in 1,000 solution or a correspondingly smaller volume of 1 in 500 solution. Aqueous solutions of dibucaine hydrochloride should be prepared with distilled water, as the salts present in tap water of many localities may precipitate the free base. Alkali-free glass should be used in the preparation of its solutions. (See caution under the general article, Local Anesthetics.)

CIBA PHARMACEUTICAL PRODUCTS, INC.

**Solution Nupercaine Hydrochloride 1:200 (Buffered):** 2 cc. ampuls.

**Solution Nupercaine Hydrochloride 1:1,000:** 5 cc. and 25 cc. ampuls.

**Solution Nupercaine Hydrochloride 1:1,500 in 0.5% Sodium Chloride:** 20 cc. ampuls.

**Solution Nupercaine Hydrochloride 1:1,000, with Epinephrine, 1:100,000:** 2 cc. and 5 cc. ampuls.

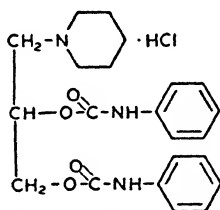
**Solution Nupercaine Hydrochloride 2%.**

**Tablets Nupercaine Hydrochloride:** 50 mg.

U. S. patent 1,825,623. U. S. trademark 266,366.

**DIPERODON HYDROCHLORIDE**—Diothane Hydrochloride—Merrell.—Diperodon—The *di*-Phenylurethane of 1-Piperidinopropane-2,3-diol Hydrochloride. — Diperodon is obtained by combining piperidine and glycerol monochlorohydrin in the presence of an alkali, and reacting the piperidinopro-

pancidol with phenyl isocyanate. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Nearly similar to those of cocaine, but it is claimed that the anesthesia lasts somewhat longer than that induced by corresponding doses of cocaine hydrochloride or procaine hydrochloride. Its toxicity by intravenous injection is about three times that of procaine hydrochloride and hence it should not be injected except in small amounts. Dipiperon hydrochloride is also available as a cream for topical use as a surface anesthetic and analgesic. It is claimed to be useful for the relief of surface pain and irritation in abrasions of the skin and mucous membranes, following hemorrhoidectomy and for the relief of pain in nonoperable cases of hemorrhoids.

Solutions of dipiperon hydrochloride prepared extemporaneously should be used promptly, since such solutions usually contain traces of alkali and are thereby subject to precipitation.

**Dosage.**—A 1 per cent solution is applied to mucous membranes; 0.5 per cent solutions may be injected. (See caution under the general article, Local Anesthetics.) The cream is rubbed into the affected area, a second thin coating applied, and covered with dressings within ten or fifteen minutes.

THE WM. S. MERRELL COMPANY

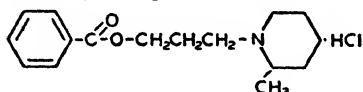
**Diothane Hydrochloride (Crystals):** bulk.

**Solution Diothane Hydrochloride 0.5% with Sodium Chloride 0.6%:** 6 cc. ampuls.

**Solution Diothane Hydrochloride 1%:** A solution of Diothane Hydrochloride, 1 per cent, in distilled water.

U. S. patent 2,004,132 (June 11, 1935; expires 1952). U. S. trademark 296,850.

**METYCAINE HYDROCHLORIDE-Lilly.**—Racemic-3-Benzoyloxy-1-(2-methylpiperidino)-propane Hydrochloride. The structural formula may be represented as follows:



For tests and standards, see Section B.



**Actions and Uses.**—Metycaine hydrochloride is a local anesthetic which produces prompt anesthesia either by subcutaneous injection or topical application to mucous membranes and similar surfaces. Pharmacologic studies on animals indicate that its toxicity following subcutaneous injection is lower than that of cocaine and comparable to that of procaine; intravenously, it was found to be approximately three times as toxic as procaine. It is considered the approximate equivalent of procaine for spinal anesthesia.

**Dosage.**—For application to the eye Metycaine Hydrochloride is used in 2 to 4 per cent solutions; for nose and throat, 2 to 10 per cent; for the urethra, 1 to 4 per cent; for infiltrative anesthesia, 0.5 to 1 per cent; for nerve block, 1 to 2 per cent; for spinal anesthesia, 1.5 to 5 per cent with a maximum quantity of drug of 0.75 mg. per pound of body weight to an absolute maximum of 150 mg. (See caution under the general article, Local Anesthetics.)

ELI LILLY AND COMPANY

**Metycaine Hydrochloride (Powder):** 15 Gm. and 120 Gm. bottles.

**Ointment Metycaine Hydrochloride 5%:** Metycaine Hydrochloride 5 per cent in a base consisting of white petrolatum with white wax and wool fat.

**Ophthalmic Ointment Metycaine Hydrochloride 4%:** Metycaine Hydrochloride 4 per cent, in a base consisting of liquid petrolatum, wool fat and with small amounts of paraffin, white petrolatum and ceresin.

**Solution Metycaine Hydrochloride 1.5%:** 200 cc. ampul-bottles. Each cubic centimeter contains 15 mg. of Metycaine Hydrochloride in Ringers' solution. For caudal anesthesia.

**Solution Metycaine Hydrochloride 20%:** 5 cc. ampuls. Each 5 cc. contains Metycaine Hydrochloride 1 Gm. in distilled water. To be used for infiltration and regional anesthesia. The solution must be diluted before using.

**Solution Metycaine Hydrochloride 2%:** 30 cc. bottles. Metycaine Hydrochloride 2 per cent in Ringer's solution containing chlorbutanol 0.5 per cent as preservative.

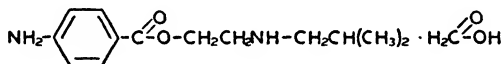
**Solution Metycaine Hydrochloride in Ringer's Solution (For Spinal Anesthesia):** 1.5 per cent, 5 cc. and 20 cc. ampuls; 2 per cent, 30 cc. vials; 5 per cent, 3 cc. ampuls.

**Tablets Metycaine Hydrochloride:** 0.15 Gm.

U. S. patent 1,784,903 (Dec. 16, 1930; expires 1947). U. S. trademark 305,894.

**BUTETHAMINE FORMATE—Monocaine Formate—Novocol.**—2-Isobutyl-amino-ethyl *p*-aminobenzoate formate.—

2-*p*-Aminobenzoxy-N-isobutylethylamine formate.—The formic acid salt of the ester formed from *p*-aminobenzoic acid and the N-isobutyl derivative of ethanolamine. The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Butethamine Formate is proposed for use in spinal anesthesia. Its action is qualitatively identical with that of procaine, but quantitatively it may produce about one-third greater anesthetic and toxic effect. For this reason approximately only three fourths of the amounts usually employed for procaine can be given with an equal degree of safety and anesthesia.

*Dosage.*—As with the use of other agents for spinal anesthesia the dosage is dependent on the speed and mode of injection, the size of the patient and the length of the operative procedure to be performed. As already indicated, the dosage of monocaine should correspond to about three fourths of that ordinarily employed for procaine.

NOVOCOL CHEMICAL MFG. CO., INC.

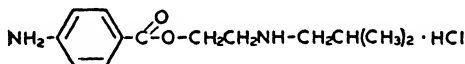
**Monocaine Formate (Crystals):** 50, 100, 150 and 200 mg. ampuls; 300 and 500 mg. containers (fractional doses). For spinal anesthesia.

**Solution Monocaine Formate 5%:** 2 cc. ampuls for spinal anesthesia. Each cubic centimeter contains 50 mg. of Monocaine Formate in sterile distilled water.

U. S. patent. 2,139,818 (Dec. 13, 1938; expires 1955).

U. S. trademark 353,653.

**BUTETHAMINE HYDROCHLORIDE — Monocaine Hydrochloride-Novocol.**—2-Isobutylamino-ethyl *p*-aminobenzoate hydrochloride.—2-*p*-Aminobenzoxy-N-isobutyl-ethylamine hydrochloride.—The hydrochloride of the ester formed from *p*-aminobenzoic acid and N-isobutyl ethanolamine. The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Butethamine hydrochloride is a local anesthetic similar to procaine hydrochloride. It is used for nerve block anesthesia in dentistry or other surgical operations. Present evidence does not warrant recommendation for its use for topical or surface anesthesia of mucous or other membranes. Its

effects, either with or without the addition of epinephrine hydrochloride, are qualitatively identical in every respect with those of procaine. Quantitatively, monocaine has been shown to have about one-third more anesthetic and toxic potency than procaine (i. e., monocaine solutions of three-fourths the concentration of procaine solutions are approximately equivalent).

**Dosage.**—For dental or other minor surgery, a 1 per cent solution with epinephrine 1:75,000 may be injected to obtain nerve block anesthesia. In major surgery or other procedures requiring nerve block anesthesia equivalent to that produced by 2 per cent procaine, a 1.5 per cent solution of butethamine with epinephrine 1:100,000 may be used. (See caution under the general article Local Anesthetics.)

NOVOCOL CHEMICAL MFG. CO., INC.

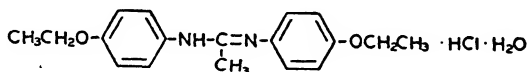
**Solution Monocaine Hydrochloride 1% with Epinephrine 1:75,000:** 2 cc., 3 cc. and 5 cc. ampuls; 2 cc., 2.5 cc. and 5 cc. Anestubes (syringe cartridge); 2½ cc. and 5 cc. Novampuls (ampul type syringe); and 30 cc., 60 cc. and 120 cc. bottles. Each cubic centimeter contains Monocaine Hydrochloride 10 mg., epinephrine U. S. P. 0.013 mg., sodium bisulfite 2.0 mg. and sodium chloride 6.5 mg. in sterile distilled water.

**Solution Monocaine Hydrochloride 1½% with Epinephrine 1:100,000:** 2 cc., 3 cc. and 5 cc. ampuls; 1 cc., 2 cc., 2½ cc. and 5 cc. Anestubes (syringe cartridge); 2½ cc. and 5 cc. Novampuls (ampul type syringe); 60 cc. and 120 cc. bottles. Each cubic centimeter contains Monocaine Hydrochloride 15 mg., epinephrine U. S. P. 0.01 mg., sodium bisulfite 2.0 mg. and sodium chloride 4.5 mg. in sterile distilled water.

U. S. patent 2,139,818 (Dec. 13, 1938; expires 1955).

U. S. trademark 353,653.

**PHENACAINE HYDROCHLORIDE—U. S. P.—Holo-caine Hydrochloride—Winthrop-Stearns.**—bis-*p*-Ethoxyphenylacetamidine.—“When dried at 105° C. for 6 hours, contains not less than 87.5 per cent and not more than 90.5 per cent of phenacaine base (C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>), corresponding to not less than 98 per cent of C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>·HCl.” U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Phenacaine Hydrochloride.

**Actions and Uses.**—Phenacaine hydrochloride is a local anesthetic like cocaine, but having the advantage of a quicker effect. A quarter of a cubic centimeter of a 1 per cent solution when instilled into the eye is usually sufficient to cause anesthesia

in from one to ten minutes. This is preceded by temporary smarting.

**Dosage.**—It is applied in a 1 per cent aqueous solution. Phenacaine hydrochloride is incompatible with alkalis and their carbonates and the usual alkaloidal reagents. Glass vessels should be avoided in preparing the solution, porcelain being used instead. The solutions are stable, as the drug is itself antiseptic. They are not injured by boiling.

MANHATTAN EYE SALVE COMPANY, INC.

**Ointment Holocaine 1%:** Collapsible ophthalmic tubes. Holocaine (phenacaine hydrochloride) 1 per cent; water, 1 per cent; wool fat, 5 per cent and petrolatum, sterile, 93 per cent.

**Ointment Holocaine and Adrenalin:** Collapsible ophthalmic tubes. Composed of holocaine (phenacaine hydrochloride), 1 per cent; adrenalin chloride solution, 2 per cent; water, 1 per cent; wool fat, 10 per cent; white petrolatum, sterile, 86 per cent.

WERNER DRUG & CHEMICAL CO.

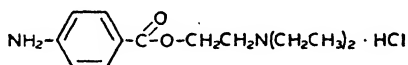
**Phenacaine Hydrochloride (Powder):** bulk and 1 Gm., 5 Gm., 30 Gm., 125 Gm. and 500 Gm. packages.

WINTHROP-STEARNs, INC.

**Holocaine Hydrochloride (Powder):** bulk. Phenacaine hydrochloride.

U. S. trademark 32,210 (Chemical Foundation, Inc.).

**PROCAINE HYDROCHLORIDE-U. S. P.**—Novocain-Winthrop-Stearns.— $\beta$ -diethylamino *p*-aminobenzoate hydrochloride. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Procaine Hydrochloride and The National Formulary under Procaine Hydrochloride Ampuls Procaine Hydrochloride Solution and Procaine Hydrochloride Tablets.

**Actions and Uses.**—Procaine hydrochloride is a local anesthetic, less toxic than cocaine and most other cocaine substitutes. When injected subcutaneously it exerts a prompt and powerful anesthetic action, but the effect is not sustained. This may be remedied by the simultaneous injection of epinephrine. Procaine hydrochloride is only slightly irritant.

It is relatively ineffective when applied to intact mucous membranes. It is probably the safest agent employed for spinal anesthesia. A special dosage form of procaine hydrochloride may

also be used to induce continuous caudal analgesia for use in obstetric cases, *provided the procedure is carried out with great care and caution and is undertaken only by skilled specialists. It is not a procedure for untrained hands.* (See caution under the general article, Local Anesthetics.)

**Dosage.**—For infiltration anesthesia, solutions of 0.25 Gm. procaine hydrochloride in 50 or 100 cc. isotonic solution of sodium chloride, with 0.3 or 0.6 cc. of epinephrine hydrochloride solution (1 in 1,000) for instillations and injections, solutions of 0.1 Gm. procaine hydrochloride in 5 or 10 cc. isotonic solution of sodium chloride, with or without 0.6 cc. of epinephrine hydrochloride solution (1 in 1,000). In ophthalmology, 1 to 5 or even up to 10 per cent solutions, and in rhinolaryngology 5 to 20 per cent solutions are recommended, with the addition of 0.4 to 0.5 cc. of epinephrine hydrochloride solution (1 in 1,000) to each 10 cc. For spinal anesthesia concentrations of 5 per cent or less are considered safe; the total amount injected at one time should not exceed 200 mg. of the drug.

#### ABBOTT LABORATORIES

**Procaine Hydrochloride (Crystals):** bulk.

**Procaine Hydrochloride for Spinal Anesthesia (Crystals):** 50 mg., 100 mg., 120 mg., 150 mg., 200 mg. and 500 mg. ampuls.

**Solution Procaine Hydrochloride 1%:** 100 cc. bottle. Each cc. contains procaine hydrochloride 10 mg., sodium chloride 6 mg., sodium bisulfite 1 mg. and distilled water.

**Solution Procaine Hydrochloride 1%:** 1.5 cc. ampuls. Each ampul contains procaine hydrochloride 15 mg. in chemically pure water with sodium chloride sufficient to make an isotonic solution.

**Solution Procaine Hydrochloride 1½%:** 250 cc. bottles. Each 100 cubic centimeters contains procaine hydrochloride 1.5 Gm.

**Solution Procaine Hydrochloride 2%:** 1 cc. and 5 cc. ampuls. Each cc. contains procaine hydrochloride 20 mg. and sodium chloride 5 mg. in distilled water to make an isotonic solution.

**Solution Procaine Hydrochloride 2%:** 100 cc. vials. Each cc. contains procaine hydrochloride 20 mg., sodium chloride 4.4 mg., sodium bisulfite 1 mg. in sterile distilled water.

**Solution Procaine Hydrochloride 5%:** 10 cc. ampuls. Each 10 cc. contains procaine hydrochloride 0.5 Gm. in water with 0.1 per cent sodium thiosulfate.

**Solution Procaine Hydrochloride 20% :** 5 cc. ampuls. Each 5 cc. contains procaine hydrochloride 1 Gm. in water with 0.1 per cent sodium thiosulfate.

**Solution Procaine Hydrochloride 10% for Spinal Anesthesia:** 2 cc. ampuls. Each cc. contains procaine hydrochloride 0.1 Gm. in distilled water.

**Solution Procaine Hydrochloride 2% with Epinephrine 1:25,000:** 1 cc. ampuls. Each cc. contains procaine hydrochloride 20 mg., epinephrine hydrochloride 0.04 mg., sodium bisulfite 1 mg. and potassium sulfate 9 mg., in distilled water to make an isotonic solution.

**Solution Procaine Hydrochloride 2% with Epinephrine 1:25,000:** 100 cc. bottles. Each cc. contains procaine hydrochloride 20 mg., epinephrine hydrochloride 0.04 mg., sodium bisulfite 1 mg. and potassium sulfate 9 mg., in distilled water to make an isotonic solution.

**Tablets Procaine Hydrochloride:** 70 mg., 0.15 Gm. and 0.2 Gm. One tablet dissolved in 4 cc., 8 cc. or 10 cc. of distilled water respectively, makes a 2 per cent solution of procaine hydrochloride.

**Hypodermic Tablets Procaine Hydrochloride:** 20 mg.

**Hypodermic Tablets Procaine Hydrochloride 20 mg. with Epinephrine 0.04 mg.:** Each contains procaine hydrochloride 20 mg., epinephrine 0.04 mg. and sodium chloride sufficient so that when the tablet is dissolved in 1 cc. of water, the resulting solution is approximately isotonic and contains 2 per cent procaine hydrochloride and 1 : 25,000 epinephrine hydrochloride.

BARRY BIOLOGICAL LABORATORY, DIVISION OF BARRY LABORATORIES, INC.

**Solution Procaine Hydrochloride 2%:** 30 cc. bottles. Each cc. contains procaine hydrochloride 20 mg., sodium chloride 4.4 mg., sodium bisulfite 1.0 mg. and 0.5 per cent chlorobutanol.

**Solution Procaine Hydrochloride 2% with Epinephrine Hydrochloride 1:25,000:** 30 cc. bottles. Each cc. contains procaine hydrochloride 20 mg., epinephrine hydrochloride 0.04 mg. and sodium chloride in distilled water to make an isotonic solution, with sodium bisulfite 1 mg. and chlorobutanol 0.5 per cent as preservatives.

GEORGE A. BREON & COMPANY

**Solution Procaine Hydrochloride 2% :** 2 cc. ampuls. Each cc. contains 20 mg. in isotonic solution of sodium chloride.

**Solution Procaine Hydrochloride 2%:** 30 cc. vials. Each cc. contains 20 mg. procaine hydrochloride in isotonic solution

of sodium chloride with chlorobutanol 0.5 per cent as a preservative.

BREWER & Co., INC.

**Solution Procaine Hydrochloride 2% with Epinephrine 1:25,000:** 30 cc. vials. Each cc. contains procaine hydrochloride 20 mg., epinephrine 0.04 mg. and sodium chloride 3.7 mg. in water, with sodium bisulfite 0.1 per cent and chlorobutanol 0.5 per cent as preservatives.

BRISTOL LABORATORIES, INC.

**Solution Procaine Hydrochloride 2%:** 1 cc. ampuls. Each cc. contains 20 mg. procaine hydrochloride, chlorobutanol 5 mg. in isotonic solution of sodium chloride.

**Solution Procaine Hydrochloride 1% with Epinephrine 1:25,000:** 3 cc. ampuls. Each cc. contains procaine hydrochloride 10 mg. epinephrine hydrochloride 0.04 mg., chlorobutanol 5 mg. and sodium bisulfite 1 mg. in isotonic solution of sodium chloride.

THE DRUG PRODUCTS Co., INC.

**Solution Procaine Hydrochloride 2%:** 2 cc. hyposols. Each cc. contains 20 mg. of procaine hydrochloride in isotonic solution of sodium chloride.

ENDO PRODUCTS, INC.

**Solution Procaine Hydrochloride 2%:** 2 cc. ampuls. Each cc. contains 20 mg. of procaine hydrochloride, 5 mg. of chlorobutanol and 1 mg. of sodium bisulfite in distilled water.

**Solution Procaine Hydrochloride 2%:** 30 cc. and 100 cc. vials. Each cc. contains 20 mg. procaine hydrochloride, 5 mg. of chlorobutanol and 1 mg. of sodium bisulfite in distilled water.

**Solution Procaine Hydrochloride 2% with Epinephrine 1:25,000:** 30 cc. and 100 cc. vials. Each cc. contains 20 mg. of procaine hydrochloride, 0.04 mg. of epinephrine, 5 mg. of chlorobutanol and 1 mg. of sodium bisulfite in distilled water.

LAKESIDE LABORATORIES, INC.

**Procaine Hydrochloride 2%:** 30 cc. and 100 cc. vials. Each cc. contains procaine hydrochloride 20 mg., sodium bisulfite 1 mg. and chlorobutanol 5 mg. in isotonic sodium chloride solution.

LINCOLN LABORATORIES, INC.

**Solution Procaine Hydrochloride 2%:** 100 cc. vials. Each cc. contains procaine hydrochloride 2 per cent in distilled water. Preserved with chlorobutanol 0.5 per cent.

MERCK & Co., INC.

**Procaine Hydrochloride (Crystals):** bulk.

THE W. M. S. MERRELL CO., LOESER LABORATORY DIVISION

**Solution Procaine Hydrochloride 1%:** 1 cc. and 10 cc. ampuls. Each cc. contains procaine hydrochloride 10 mg. in isotonic solution of sodium chloride.

**Solution Procaine Hydrochloride 1%:** 30 cc. and 100 cc. Each cc. contains procaine hydrochloride 10 mg. in isotonic solution of sodium chloride with chlorobutanol 0.5 per cent as a preservative.

**Solution Procaine Hydrochloride 2%:** 30 cc. and 100 cc. Each cc. contains procaine hydrochloride 20 mg. in isotonic solution of sodium chloride with chlorobutanol 0.5 per cent as a preservative.

**Solution Procaine Hydrochloride 2%:** 1 cc. and 10 cc. ampuls. Each cc. contains procaine hydrochloride 20 mg. in isotonic solution of sodium chloride. 40 cc. and 160 cc. bottles.

E. S. MILLER LABORATORIES, INC.

**Solution Procaine Hydrochloride 1%:** 30 cc., 50 cc. and 100 cc. vials and 2 cc. and 5 cc. ampuls. Vials preserved with 0.5 per cent chlorobutanol.

**Solution Procaine Hydrochloride 2%:** 30 cc., 50 cc. and 100 cc. vials and 2 cc. and 5 cc. ampuls. Vials preserved with 0.5 per cent chlorobutanol.

E. R. SQUIBB & SONS

**Procaine Hydrochloride for Spinal Anesthesia (Crystals):** 50 mg., 100 mg., 120 mg., 150 mg., 200 mg. and 500 mg. ampuls. Bottles of 100 Gm.

THE UPJOHN COMPANY

**Solution Procaine Hydrochloride 2%:** 30 cc. rubber capped vials and 100 cc. bottles. Each cc. contains chlorobutanol 5.0 mg., procaine hydrochloride 2.0 mg., sodium bisulfite 1.0 mg., sodium chloride 8.4 mg.

**Solution Procaine Hydrochloride 2% with Epinephrine 1:20,000:** 3 cc. ampuls. Each cc. contains procaine hydrochloride 20 mg., epinephrine 0.05 mg., sodium bisulfite 2.6 mg., benzoic acid 0.3 mg., sodium chloride 8.3 mg. and normal hydrochloric acid 0.0016 cc. in distilled water saturated with carbon dioxide.

**Solution Procaine Hydrochloride 2% with Epinephrine 1:20,000:** 30 cc. vials. Each cc. contains procaine hydrochloride 20 mg., epinephrine 0.05 mg., sodium bisulfite 2.6 mg., benzoic acid 0.3 mg., sodium chloride 8.3 mg., normal hydrochloric acid 0.0016 cc. and chlorobutanol not to exceed 5 mg. in distilled water saturated with carbon dioxide.



**Hypodermic Tablets Procaine Hydrochloride 20 mg. with Epinephrine 0.025 mg.:** Each contains procaine hydrochloride 20 mg., epinephrine 0.025 mg., sodium chloride 13 mg., benzoic acid 0.3 mg., sodium bisulfite 0.125 mg. and boric acid 2.27 mg. One tablet dissolved in 1 cc. of distilled water makes a 2 per cent solution of procaine hydrochloride.

U. S. STANDARD PRODUCTS CO.

**Solution Procaine Hydrochloride 2% with Epinephrine 1:25,000:** 1 cc. ampuls. Each cc. contains procaine hydrochloride 20 mg., epinephrine hydrochloride 0.04 mg. and sodium bisulfite 0.45 mg. in distilled water.

WINTHROP-STEARNs, INC.

**Novocain (Crystals):** bulk. Procaine hydrochloride.

**Novocain for Spinal Anesthesia (Crystals):** 50 mg., 100 mg., 120 mg., 150 mg., 200 mg., 300 mg. and 500 mg. ampuls.

**Solution Novocain 1%:** 2 cc. and 6 cc. ampuls. Each cc. contains procaine hydrochloride 10 mg., sodium chloride 6 mg. and sodium bisulfite not more than 1 mg. in distilled water.

**Solution Novocain 2%:** 3 cc. ampuls. Each cc. contains procaine hydrochloride 20 mg., sodium chloride 4 mg. and sodium bisulfite not more than 1 mg. in distilled water.

**Solution Novocain 2%:** 30 cc. bottles. Each cc. contains procaine hydrochloride 20 mg., sodium chloride 3.5 mg., sodium bisulfite 2 mg. and chlorobutanol 2.5 mg. as a preservative.

**Solution Novocain 10% for Spinal Anesthesia:** 2 cc. ampuls. Each cc. contains procaine hydrochloride 0.1 Gm. and acetone sodium bisulfite not more than 4 mg. in distilled water.

**Solution Novocain 20%:** 1.5 cc. and 5 cc. ampuls. Each cc. contains procaine hydrochloride 0.2 Gm. and sodium bisulfite not more than 5 mg. in distilled water. This solution must be diluted before use.

**Solution Novocain 1% with Suprarenin 1:100,000:** 30 cc. bottles. Each cc. contains procaine hydrochloride 10 mg., epinephrine bitartrate 0.01 mg., sodium chloride 4 mg., potassium sulfate 4 mg., sodium bisulfite not more than 2.5 mg. and chlorobutanol 2.5 mg.

**Solution Novocain 1% with Ephedrine 5%:** 1 cc. and 2 cc. ampuls. Each cc. contains procaine hydrochloride 10 mg., ephedrine hydrochloride 50 mg. and not more than 3 mg. sodium bisulfite in sterile distilled water.

**Solution Novocain 1% with 1-Suprarenin Synthetic Bitartrate 1:50,000:** 2 cc. and 6 cc. ampuls. Each cc. contains procaine hydrochloride 10 mg., synthetic epinephrine bitartrate

0.02 mg., sodium chloride 4 mg., potassium sulfate 4 mg. and sodium bisulfite not more than 1.5 mg. in distilled water.

**Solution Novocain 2% with 1-Suprarenin Synthetic Bitartrate 1:20,000:** 1 cc., 3 cc. and 6 cc. ampuls. Each cc. contains procaine hydrochloride 20 mg., synthetic epinephrine bitartrate 0.05 mg., sodium chloride 2 mg., potassium sulfate 4 mg. and sodium bisulfite not more than 1.5 mg. in distilled water.

**Solution Novocain 2% with 1-Suprarenin Synthetic Bitartrate 1:50,000:** 1 cc. and 3 cc. ampuls. Each cc. contains procaine hydrochloride 20 mg., synthetic epinephrine bitartrate 0.02 mg., sodium chloride 2 mg., potassium sulfate 4 mg. and sodium bisulfite not more than 1.5 mg. in distilled water.

**Solution Novocain 20% with 1-Suprarenin Synthetic Bitartrate 1:9,000:** 1.5 cc. and 5 cc. ampuls. Each cc. contains procaine hydrochloride 0.2 Gm. and synthetic epinephrine bitartrate 0.11 mg. and sodium bisulfite not more than 5 mg. in distilled water. This solution must be diluted before use.

**Tablets Novocain:** 65 mg.

**Hypodermic Tablets Novocaine:** 50 mg. Each contains procaine hydrochloride 50 mg. and boric acid 3 mg.

**Hypodermic Tablets Novocaine:** 0.2 Gm. Each contains procaine hydrochloride 0.2 Gm., sodium chloride 60 mg. and boric acid 16 mg.

**Hypodermic Tablets Novocaine 20 mg. with 1-Suprarenin Synthetic Bitartrate 0.02 mg.** Each contains procaine hydrochloride 20 mg., synthetic epinephrine as bitartrate 0.02 mg., boric acid 1.92 mg. and acetone sodium bisulfite not more than 0.57 mg.

**Hypodermic Tablets Novocain 20 mg. with 1-Suprarenin Synthetic Bitartrate 0.05 mg.** Each contains procaine hydrochloride 20 mg., synthetic epinephrine as bitartrate 0.05 mg., boric acid 1.33 mg. and acetone sodium bisulfite not more than 0.57 mg.

**Hypodermic Tablets Novocain 50 mg. with 1-Suprarenin Synthetic Bitartrate 0.083 mg.** Each contains procaine hydrochloride 50 mg., synthetic epinephrine as bitartrate 0.08 mg., boric acid 1.79 mg. and acetone sodium bisulfite not more than 1.06 mg.

**Hypodermic Tablets Novocain 60 mg. with 1-Suprarenin Synthetic Bitartrate 0.06 mg.** Each contains procaine hydrochloride 60 mg., synthetic epinephrine as bitartrate 0.06 mg., boric acid 3.39 mg. and acetone sodium bisulfite not more than 1.29 mg.

**Hypodermic Tablets Novocain 80 mg. with 1-Suprarenin Synthetic Bitartrate 0.06 mg.** Each contains procaine hydrochloride 80 mg., synthetic epinephrine as bitartrate 0.06 mg., boric acid 3.19 mg. and acetone sodium bisulfite not more than 1.7 mg.

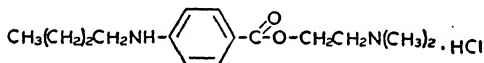
**Hypodermic Tablets Novocain 0.1 Gm. with 1-Suprarenin Synthetic Bitartrate 0.25 mg.** Each contains procaine hydrochloride 0.1 Gm., synthetic epinephrine as bitartrate 0.25 mg., boric acid 5.38 mg. and acetone sodium bisulfite not more than 2.16 mg.

**Hypodermic Tablets Novocaine 0.125 Gm. with 1-Suprarenin Synthetic Bitartrate 0.13 mg.** Each contains procaine hydrochloride 0.125 Gm., synthetic epinephrine as bitartrate 0.13 mg., boric acid 4.13 mg. and acetone sodium bisulfite not more than 2.64 mg.

U. S. patent 812,554 (Feb. 13, 1906 expired). U. S. trademark 53,072.

**TETRACAINE HYDROCHLORIDE-U. S. P.—Pontocaine Hydrochloride-Winthrop-Stearns.**—"When dried over sulfuric acid for 4 hours contains not less than 86.5 per cent and not more than 88.5 per cent of  $C_{15}H_{24}N_2O_2$ , corresponding to not less than 98.4 per cent of  $C_{15}H_{24}N_2O_2 \cdot HCl$ ." U. S. P.

The base of tetracaine hydrochloride belongs to the procaine type. It differs from procaine base in that one of the hydrogens of the paraamino group is replaced by a butyl group, and the two ethyl groups of procaine are replaced by two methyl groups in tetracaine base. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Tetracaine Hydrochloride.

**Actions and Uses.**—Tetracaine hydrochloride is a local anesthetic with actions similar to those of procaine hydrochloride, but it is effective when applied to mucous membranes in lower concentrations. (See caution under the general article, Local Anesthetics.) It is used for surface anesthesia in the eye, nose and throat, and in spinal anesthesia in which the anesthesia is prolonged.

**Dosage.**—Solution of tetracaine hydrochloride, 0.5 per cent is used in the eye; a 2 per cent solution is applied to the nose and throat. A 0.5 per cent solution is injected for spinal anesthesia, for which purpose the dose is from 2 to 4 cc. (containing from 10 to 20 mg. of the salt). A total of 20 mg. is considered the maximum safe dose for spinal injection.

For continuous caudal analgesia the appropriate dosage form of tetracaine hydrochloride is made up for 0.15 per cent solution,

e. g. 4 cc. sterile isotonic saline solution to 250 mg. and diluted further with sterile isotonic saline solution to a volume of 100 cc. An initial skin wheal is raised with the local anesthetic and the underlying tissues infiltrated so that the needle to be inserted into the sacral canal may be inserted without too much discomfort by the patient. Thirty cc. tetracaine hydrochloride 0.15 per cent solution is injected. Signs of fulness in one or both legs, progressive loss of painful sensations and relief of abdominal uterine cramps will from five to fifteen minutes indicate that the analgesic solution has produced its effects. Supplementary injections depend on the individual patient. Usually from 10 to 20 cc. of tetracaine hydrochloride 0.15 per cent solution injected at intervals of from 40 to 90 minutes are sufficient to keep the patient comfortable during the entire course of labor. In many cases approximately 100 cc. of the 0.15 per cent solution would be sufficient for the management of labor and delivery and repairs.

WINTHROP-STEARNs, INC.

**Pontocaine Hydrochloride "Niphanoid" for Spinal Anesthesia:** 10 mg. and 20 mg. Ampuls containing tetracaine hydrochloride in finely divided and instantly soluble form. The trade term "Niphanoid" (from the Greek "snow like") is applied to the process whereby dilute solutions of the drug are subjected to rapid freezing and subsequent evaporation of the solvent under high vacuum; the resultant material is claimed to be more readily soluble.

**Ophthalmic Ointment Pontocaine Base:** An ointment containing 0.5 per cent of tetracaine base, the free base of tetracaine hydrochloride, dissolved in white petrolatum.

**Solution Pontocaine Hydrochloride 1%:** 2 cc. ampuls. Each 2 cc. of solution contains tetracaine hydrochloride 20 mg., sodium chloride 13.3 mg., and acetone bisulfite 4 mg.

**Solution Pontocaine Hydrochloride 0.5%:** 15 cc. bottles. Contains 0.4 per cent chlorobutanol as a preservative.

**Solution Pontocaine Hydrochloride 2%:** 30 cc. and 120 cc. bottles. The solution contains 0.4 per cent chlorobutanol as a preservative and is tinted with methylene blue to prevent accidental use for injection.

**Tablets Pontocaine Hydrochloride:** 0.1 Gm. Each tablet contains tetracaine hydrochloride 0.1 Gm., boric acid 5 mg., acetone sodium bisulfite not more than 0.5 mg. To be used only for preparing solutions for surface anesthesia (not for injection) in rhinolaryngology, ophthalmology and dentistry.

U. S. patent 1,889,645 (Nov. 29, 1932; expires 1949). U. S. trademark 282,418.

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## CHAPTER IV

# Local Anti-Infectives

This chapter comprises antiseptics, disinfectants, antibacterials, fungicides, antiprotozoan agents, antibiotics and parasiticides that are chiefly employed for their local effect on topical application. Certain agents of this class that are administered internally, though employed for their local action, as urinary antiseptics or intestinal disinfectants, are described in the chapter on Systemic Anti-Infectives.

Criteria for evaluation of skin disinfectants (bacterial) which the Council deems advisable include:

1. Phenol coefficients or other *in vitro* tests in the absence and in the presence of serum, using both vegetative bacterial cells and clostridial spores, with suitable recovery mediums containing, if known, neutralizing substances for the disinfectant being tested.

2. Data on germicidal efficiency under conditions simulating actual use by the method of Price (Price, P. B.: *The Bacteriology of Normal Skin: A New Quantitative Test Applied to a Study of the Bacterial Flora and the Disinfectant Action of Mechanical Cleaning*, *J. Infect. Dis.* 63:301 [Nov.-Dec.] 1938; Ethyl Alcohol as a Germicide, *Arch. Surg.* 38:528 [March] 1939) or, better still, by an extension of the method of Price (Bernstein, L. H. T.: *Standardization of Skin Disinfectants*, *J. Bacteriol.* 43:50[Jan.] 1942). The complications due to possible effects of the germicide on the skin itself should be taken into consideration (Cromwell, H. W., and Leffler, Ruth: *Evaluation of "Skin Degerming" Agents by a Modification of the Price Method*, *ibid.*, p. 51).

3. Data on germicidal efficiency by an animal method, such for example as suggested by Alice H. Kempf and W. J. Nungester (An *In Vivo* Test for the Evaluation of Skin Disinfectants, *ibid.*, p. 49) or R. W. Sarber (*ibid.*, p. 50).

4. Evidence from animal experiments regarding irritant action on skin and mucosae and regarding systemic toxicity.

5. Critical clinical evidence supporting claims of harmlessness and efficacy.

6. Data on the bacteriostatic activity as distinguished from the germicidal activity of the disinfectant.

### Alcohols

**ISOPROPYL ALCOHOL.**—Propan-2-ol.—Obtained by the reduction of acetone or, as a product in the petroleum industry,

by the absorption of olefin gases containing propylene in sulfuric acid, and hydrolyzing the resulting sulfuric acid esters. The structural formula may be represented as follows:

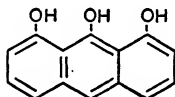


For description and standards, see The National Formulary 1st supplement under Isopropyl Alcohol and National Formulary under Isopropyl Alcohol Rubbing Compound.

**Actions, Uses and Dosage.**—Recent investigations indicate that isopropyl alcohol compares favorably with ethyl alcohol so far as anti-infective action is concerned. Isopropyl alcohol should not be relied on to destroy such spore-bearing organisms as *Clostridium tetani*, *Clostridium welchii* or *Bacillus anthracis*. It has been recommended for the disinfection of the skin and of hypodermic syringes and needles. As it is said not to affect the potency of solutions or insulin, it has been employed as a disinfecting agent in connection with the administration of this agent. Isopropyl alcohol has been used for the removal of creosote from the skin as a prophylactic agent against creosote burns. It may also be employed in rubbing compounds as an adjunct in skin massage for its rubrifacient action and as a skin conditioning agent in the care of bedfast patients. It is not potable and should not be given by mouth.

### Anthracene Derivatives

**ANTHRALIN.**—1,8,9-Anthratrion. Anthralin may be represented by the following structural formula:



For tests and standards, see Section B.

**Actions and Uses.**—Anthralin is recommended as a substitute for chrysarobin in the treatment of psoriasis, having the advantage of less liability to production of dermatitis, less tendency to produce conjunctivitis when used about the face and scalp and less tendency to discolor the skin. The preparation has also been recommended in the treatment of chronic dermatomycosis and for stimulating action in chronic dermatoses.

**Dosage.**—Anthralin is generally employed in concentrations of from 0.1 per cent up to 1.0 per cent in ointments or creams. It is always well to begin with smaller dosages because of a tendency to irritate the skin.

ABBOTT LABORATORIES

**Ointment Anthralin:** 0.1%, 0.25%, 0.5%, and 1%. Anthralin in petrolatum base.

**Anthralin Cream:** 0.1%, 0.25% and 0.5%. Anthralin in a vanishing cream base of potassium stearate, potassium oleate and distilled water.

## Antibiotics

**TYROTHRIN.**—An extract, first isolated by Dubos, obtained from *Bacillus brevis*, a gram-positive, aerobic, spore-forming soil organism. Tyrothricin possesses antibacterial action against several species of gram-positive organisms.

**Actions and Uses.**—Tyrothricin consists of at least two substances, gramicidin and tyrocidin, the former agent being by far the more active component. It seems not unlikely that some of the earlier reports which were claimed to be based on the use of gramicidin were actually concerned with the mixture. Included in the organisms that show some degree of susceptibility are species of pneumococci, streptococci and staphylococci. Its action on bacteria appears to consist, at least in part, of inhibiting enzymatic action, retarding growth and causing lysis of the bacteria against which it is effective. Its strength is determined at present by the protection afforded mice infected with pneumococci administered intraperitoneally.

Tyrothricin should be applied locally. It is ineffective when administered orally and is ineffective and dangerous when given intravenously. It has been reported to be of value in the treatment of superficial indolent ulcers, the predominating organism of which is gram positive, mastoiditis, empyema and some other wound infections. Its field of usefulness is limited and it appears to exert no effect unless it can come in direct contact with the organisms. Thus it may not exert much effect in the presence of deep-seated infections. Body fluids such as saliva, urine and serum offer a slight inhibiting action, whereas substances from gram-negative organisms are decidedly inhibiting.

It may be used with caution in body cavities as long as there is no direct connection with the blood stream. But in no instance should proper surgical treatment be ignored when it is indicated. It should be remembered that, although tyrothricin appears to have a field of usefulness in medicine, its use is still in an experimental stage and much work remains to be done before its true status is established and final comparisons can be made with other antibiotics and anti-infective agents in general. Routine or indiscriminate use of solutions of tyrothricin for irrigation of the paranasal sinuses or other infected cavities close to the subarachnoid space following surgery should be avoided because of the danger of chemical meningitis that has been reported to occur following such application of this agent.

**Dosage.**—Tyrothricin must be applied locally, *not intravenously or by mouth*. It is administered after diluting with sterile distilled water to form an isotonic solution in a concentration which yields 500 micrograms of the drug per cubic centimeter. This concentration is usually effective against the infecting or-

ganism, although higher concentrations may be used if indicated. However, higher concentrations may be irritating to the tissues.

PARKE, DAVIS & COMPANY

**Solution Tyrothricin 2% :** 10 cc. vials. Each cubic centimeter contains 20 mg. of tyrothricin in alcohol 92 per cent.

SHARP & DOHME, INC.

**Solution Tyrothricin Concentrate:** 1 cc. ampul of a solution of tyrothricin, 25 mg. per cubic centimeter, in alcohol 2 per cent and propylene glycol 75 per cent, accompanied by a vial containing 49 cc. of sterile distilled water which contains phenylmercuric borate in a concentration of 1:50,000; 10 cc. and 20 cc. ampul of a solution of tyrothricin, 25 mg. per cubic centimeter, not accompanied by a diluent.

### Cresol and Derivatives

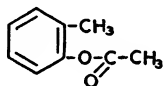
Cresols are phenols in which one of the hydrogen atoms has been replaced by  $\text{CH}_3$ . This substitution increases the germicidal efficiency, while the toxicity is not increased, at least not in the same ratio. The cresols, therefore, possess distinct advantages as disinfectants. In practice, they are much less toxic than phenol, because they are used more diluted, but they are far from being "nonpoisonous." Another advantage of the cresol preparations over phenol is their lower cost. Their disadvantages are the disagreeable odor, which depends mainly on impurities, their limited solubility in water, and their variable composition and activity.

They may be rendered soluble by the addition of soap, as in the official compound solution of cresol, and in several other ways. The variability is best discounted by the determination of the phenol coefficient.

The official cresol is a mixture of the three isomers of  $\text{C}_6\text{H}_4\text{OH.CH}_3$ . The "higher homologues," containing two or more methyl groups are generally referred to as cresylic acid. They have a higher phenol coefficient.

The toxicity and local actions of the cresols, as of other phenols, may be diminished by "masking" the active OH group by the formation of esters.

**meta-CRESYLACETATE.**—Cresatin-Sulzberger-Sharp & Dohme. The structural formula of *meta*-cresylacetate may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—*meta*-Cresylacetate is said to possess anti-



septic and analgesic properties, and is apparently free from toxic effects. It is said to be useful in the treatment of affections of the nose, throat and ear, such as follicular tonsillitis, nasal suppuration due to ethmoid diseases, atrophic nasopharyngeal catarrhs, furunculosis of the external auditory canal and purulent otitis media. When applied to mucous membranes it is said to cause no irritation, sloughing or discomfort.

*Dosage.*—*meta-Cresylacetate* may be employed either in the pure form or in dilution with oils or alcohol by direct application or spray.

SHARP & DOHME, INC.

**Cresatin Metacresylacetate Sulzberger:** Supplied in 30 cc. glass stoppered bottles.

**Ointment Cresatin Metacresylacetate Sulzberger:** 7.1 Gm. tubes. Contains metacresylacetate 80 per cent, with benzoic acid and ethyl-cellulose.

U. S. patent 1,031,971 (July 9, 1912; expired). U. S. trademark 80,533.

### Surface Active Anti-Infectives

The local anti-infectives belonging to this group are substances which have the property of altering the physical properties of surface or interfaces. They are sometimes referred to as "detergents." They are usually subclassified as anionic, cationic or nonionic accordingly as they are negatively or positively charged or are unchanged on the chemical group of the compound that is responsible for the surface activity.

The members of the cationic group have far greater anti-infective action than have those of the other two groups. They are represented by fatty amine salts, the quaternary ammonium compounds, and the alkyl pyridinium compounds. The anion-active group is exemplified by ordinary soap, a true detergent, alkyl sulfates and salts of bile acids. The nonionic agents possess no significant germicidal activity and some may actually stimulate the growth of bacteria. The partial esters of polyhydric alcohols and fatty acids are representative of this class.

The mechanism whereby some surface active agents act as anti-infectives is not yet clearly understood. Attempts have been made to correlate the ability of these compounds to reduce surface tension with their anti-infective action. That this factor alone is not responsible for the bactericidal action of these compounds is apparent from the fact that many substances which are good surface tension depressors are poor anti-infectives. Also, at the concentrations at which the surface active agents act as anti-infectives, the surface tension does not differ appreciably from that of a good culture medium. Evidence is accumulating that these compounds function as anti-infectives by virtue of their ability to denature proteins and possibly because of their cytolytic activity.

The anti-infective action varies with the chemical constitution of these compounds and the pH to which they are adjusted. In general, the anionic agents are bactericidal only against gram-positive organisms; cationic agents are effective against both gram-positive and gram-negative organisms but higher concentrations are required to kill the latter type. Anionic agents work best in a more acid medium, whereas the anti-infective power of cationic agents increases as the pH is increased though in some instances the increase is not very great. The bactericidal action of surface active anti-infectives is reduced in the presence of serum, so that their phenol coefficient tested by methods not involving the addition of organic matter are subject to erroneous interpretation when applied to conditions of actual use.

### *Anionic*

**SODIUM TETRADECYL SULFATE.**—See section on Sclerosing Agents.

### *Cationic Surface Active Anti-Infectives*

Cationic surface active anti-infectives bear positive electrical charges on their hydrophobic groups. Most of the commonly available anti-infectives belonging to this group are supplied at a pH slightly under 7.0. Since the bactericidal action of cationic compounds is opposed by that of anionic agents (soap in concentrations as low as 0.1 per cent is harmful), their application to the intact skin to be prepared for surgery has to be preceded by thorough rising of the soap-cleaned areas, first with water and then with 70 per cent alcohol. The use of alcohol diminishes the ionization of ordinary soap solution, so that the inactivating chemical union of soap with the disinfection is prevented.

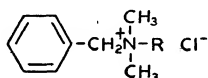
The quaternary ammonium compounds form a film on skin under which organisms may remain viable.

Cationic detergents cannot be expected to provide positive disinfection of surgical instruments and rubber articles, since like most other types of disinfectants, they possess little sporicidal activity. They may, however, be used for preservation of previously sterilized articles during storage. Manufacturers of Council accepted cationic disinfecting agents recommending such use are required to include on labels and in advertising a disclaimer of action against clostridial spores.

Some of the fatty amine salts appear to be primary irritants or skin sensitizers. Many of the quaternary ammonium compounds and the alkyl pyridinium compounds have been used as local anti-infectives for several years and very few instances of skin hypersensitivity have been reported.

**BENZALKONIUM CHLORIDE-U. S. P.**—Zephiran Chloride-Winthrop-Stearns. — Alkylbenzyl dimethyl Ammonium Chloride.—“A mixture of alkyl dimethyl benzyl ammonium

chlorides of the general formula  $C_6H_5CH_2N(CH_3)_2RCl$ , in which R represents a mixture of the alkyls from  $C_8H_{17}$  to  $C_{18}H_{37}$ . It contains, when calculated on a moisture-free basis and the average molecular weight of 366, not less than 97 per cent and not more than 102 per cent of  $C_6H_5CH_2N(CH_3)_2RCl$ ." U. S. P. The structural formula of benzalkonium chloride may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Benzalkonium Chloride and Benzalkonium Chloride Solution.

*Actions and Uses.*—Benzalkonium chloride when employed in solutions of the proper dilution is an effective, relatively non-injurious, surface disinfectant which is germicidal for many pathogenic nonsporulating bacteria and fungi after several minutes' exposure. Solution of benzalkonium chloride have low surface tension and possess detergent, keratolytic and emulsifying actions, properties which favor penetration and wetting of tissue surfaces.

They are said to be emollient and relatively nonirritating in effective concentrations. Solutions are of comparatively low toxicity under the conditions of use for which they are recommended. Rabbits tolerate from 3 to 5 cc. by mouth or 1.2 cc. subcutaneously or intraperitoneally per kilogram of body weight of a 1 per cent aqueous solution. Application to the skin of these animals, of various concentrations, show that a 0.1 per cent solution is the highest concentration that may be allowed to remain in contact for twenty-four hours without producing irritation.

Benzalkonium chloride is suitable for general use in the prophylactic disinfection of the intact skin and mucous membranes and in the treatment of superficial injuries and infected wounds in solutions ranging in concentration from 1:40,000 to 1:1,000. It is also used for the preservation of sterilized surgical instruments and rubber articles during storage. Sodium nitrite 0.5 per cent is added to benzalkonium chloride solutions for the storage of metal instruments to prevent corrosion.

*Dosage.*—For the preoperative disinfection of the unbroken skin or the treatment of superficial injuries and fungous infections benzalkonium chloride tincture 1:1,000 (tinted or stainless according to preference) is recommended. Benzalkonium chloride solution is employed in concentrations of from 1:10,000 to 1:2,000 for the preoperative disinfection of mucous membranes and denuded skin, from 1:5,000 to 1:2,000 for instillation and irrigation of the eye or vagina, and from 1:10,000 to 1:5,000 for widely denuded surfaces. For urinary bladder and urethral

irrigation a concentration of not more than 1:20,000 of the aqueous solution is recommended; for retention lavage of the bladder, a concentration not to exceed 1:40,000 should be used. For therapeutic disinfection of deep lacerations the undiluted 1:1,000 aqueous solution may be employed, but for the irrigation of infected deep wounds, concentrations not to exceed 1:3,000 should be used. For the treatment of infected widely denuded areas with wet dressings, the aqueous solution should be used in concentrations of 1:5,000 or less.

For the sterile storage of metallic instruments and rubber articles, benzalkonium chloride solution 1:1,000 is used. For the disinfection of operating room equipment a 1:5,000 concentration of the solution may be employed.

WINTHROP-STEARNs, INC.

**Solution Zephiran Chloride 1:1,000:** 0.24 liter and 3.8 liter bottles. A distilled water solution of benzalkonium chloride 0.1 per cent.

**Solution Zephiran Chloride 1:1000:** 14.8 cc. bottles.

**Solution Zephiran Chloride 12.8% (Concentrate):** 118 cc. and 3.79 liter bottles. A concentrated solution of benzalkonium chloride which may be diluted with water or isotonic salt solution before use.

**Zephiran Tint:** 1.81 Gm. vials, D and C red No. 39, for use in the preparation of colored benzalkonium chloride solutions.

**Tincture Zephiran Chloride 1:1,000 (Stainless):** 0.24 liter and 3.8 liter bottles. An alcohol-acetone-aqueous solution containing 0.1 per cent (W/V) benzalkonium chloride, ethyl alcohol 50 per cent and acetone 10 per cent by volume.

**Tincture Zephiran Chloride 1:1,000 (Tinted):** 0.24 liter and 3.8 liter bottles. An alcohol-acetone-aqueous solution containing 0.1 per cent (W/V) of benzalkonium chloride, ethyl alcohol 50 per cent and acetone 10 per cent by volume, colored with certified dye (D & C Red No. 39).

U. S. patents 2,086,585, 2,087,131 and 2,087,132 (July 13, 1937; expire 1954) and 2,108,765 and 2,113,606 (Feb. 15, 1938 and April 12, 1938; expire 1955); 2,152,047 (March 28, 1939; expires 1956), U. S. trademark 333,899.

**CETYL PYRIDINIUM CHLORIDE.—Ceepryn Chloride-Merrell.**—The monohydrate of the quaternary salt of pyridine and cetyl chloride.

For tests and standards, see Section B.

**Actions and Uses.**—Cetyl pyridinium chloride, a quaternary ammonium salt, is a cationic detergent that possesses useful surface-active as well as antiseptic properties. It is employed in aqueous solution or tincture in appropriate dilutions for topical application in the pre-operative disinfection of the intact skin and

the prophylactic antiseptics of superficial minor wounds. It is also useful by topical application or irrigation for therapeutic disinfection of accessible mucous membranes and more extensive wounds or infections of the underlying tissues. It may also be used to preserve sterility of instruments during storage.

Cetyl pyridinium chloride is subject to the shortcomings of other cationic detergents employed as germicides in that its action is opposed by anionic detergents such as ordinary soap, may be reduced in the presence of serum and tissue fluids, and is not reliable against clostridial spores.

**Dosage.**—For pre-operative preparation of the intact skin, a 1:100 aqueous solution may be used alone for scrubbing for a period of five to ten minutes; when the conventional soap-alcohol-ether-germicide method is to be employed, 1:500 or 1:1000 tincture dilutions may be used as the germicide if soap is thoroughly removed before application. Similar dilutions of the tincture or a 1:1000 aqueous solution may be used for topical application to minor lacerations and abrasions. For disinfection of delicate mucous membranes or extensive areas of exposed tissue, from 1:5000 to 1:10,000 solutions should be used.

WM. S. MERRELL COMPANY

**Isotonic Solution Ceepryn 1:1000:** 480 cc. and 3.84 liter bottles. Contains 0.1 per cent cetyl pyridinium chloride in distilled water made isotonic by addition of 0.26 Gm. of monobasic sodium phosphate and 1.43 Gm. of disodium phosphate per 100 cc.

**Concentrated Solution Ceepryn 10%:** 180 cc. and 3.84 liter bottles. An aqueous solution containing 10 Gm./100 cc. of cetyl pyridinium chloride and 8 Gm./100 cc. of monobasic sodium phosphate for the preparation of solutions and tinctures for external use.

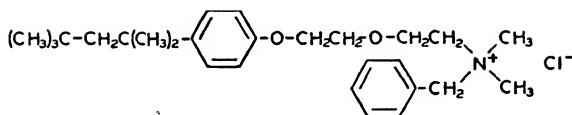
**Tincture Ceepryn 1:200 (Tinted):** 120 cc., 480 cc. and 3.84 liter bottles. Contains 0.5 per cent of cetyl pyridinium chloride in a tincture medium of 50 per cent ethyl alcohol by volume and 10 per cent acetone by volume.

**Tincture Ceepryn 1:500 (Tinted or Untinted):** 120 cc., 480 cc. and 3.84 liter bottles. Contains 0.2 per cent of cetyl pyridinium chloride in a tincture medium of 50 per cent ethyl alcohol by volume and 10 per cent acetone by volume.

**Tincture Ceepryn 1:1000 (Tinted):** 120 cc., 480 cc., and 3.84 liter bottles. Contains 0.1 per cent cetyl pyridinium chloride in a tincture medium of 50 per cent ethyl alcohol by volume and 10 per cent acetone by volume.

U. S. patent 2,295,504; U. S. trademark 398,185.

**BENZETHONIUM CHLORIDE—Phemerol Chloride-Parke, Davis.**—[p-(2-methyl-4,4-dimethyl pentane-2) (phenoxy-ethoxy-ethyl)]-dimethylbenzylammonium chloride monohydrate. Benzethonium chloride has the following structural formula:



For tests and standards, see Section B.

**Actions and Uses.**—Benzethonium chloride is a synthetic quaternary ammonium compound belonging to the cationic group of detergents, and has been shown to exert an inhibitory effect on the metabolism and viability of commonly occurring bacteria and fungi. Tincture benzethonium chloride 1:500 and solution benzethonium chloride 1:1,000 (aqueous) are proposed as general purpose germicides and antiseptics.

**Dosage.**—Both the tincture and the solution are used full strength except in the nose and eye. For use in the nose and eye only the solution should be used, diluted with four parts of water.

PARKE, DAVIS & COMPANY

**Solution Phemerol Chloride 1:1,000:** 30 cc., 120 cc., 480 cc. and 3,840 cc. bottles.

**Tincture Phemerol Chloride 1:500:**

U. S. Patent 2,115,250 (expires April 26, 1955). U. S. trademark: 305,545.

## Dyes

Dyes are used medically as antiseptics, as chemotherapeutic agents and for special effects upon tissue cells. The local antiseptic action of dyes can be explained by their bacteriostatic and bactericidal powers. These are often relatively specific.

The dyes which have been introduced in medicine, for the most part in the last decade, are practically all organic synthetics. Roughly they may be divided into five classes: (1) the azo dyes, of which scarlet red medicinal, scarlet red sulfonate and dimazon are described in New and Nonofficial Remedies (these have been in use for considerable time); (2) the acridine dyes, such as acriflavine hydrochloride (introduced as "acriflavine"), acriflavine base (introduced as "neutral acriflavine"), and proflavine; (3) the fluorescein dyes, either as fluorescein or combined with the metal mercury, such as mercurochrome soluble and flumerin; (4) the phenolphthalein dyes such as phenolphthalein and phenolsulfonphthalein, which are official in the U. S. Pharmacopeia, and the chlorine, bromine and iodine substitution products; (5) the triphenylmethane or rosaniline series, which comprise a large list of substances used in the industries, extensively in laboratory practice and more recently in medicine, such as gentian violet, crystal violet, methyl violet and fuchsin; (6) miscellaneous dyes, such as methylene blue (methylthionine chloride-U. S. P.). Much confusion has existed

concerning the composition of dyes, various manufacturers of commercial dyestuffs making similar dyes of varying composition both qualitatively and quantitatively; usually the commercial dye contains a diluent, such as dextrin or salts, and is judged by tinctorial power. In order to obtain comparable results when employed clinically, the dyes should be of constant composition, preferably without diluent.

### Azo Compounds

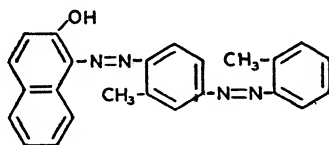
The azo dyes have been used in medicine for many years—more generally recalled under the name “scarlet R” (scarlet red). The exact constitution of the “scarlet R” dyes which have been used seems to have varied in minor details with different investigators. Chemically they have been azo compounds (that is, they contain the linkage—N:N—) combined with betanaphthol. In New and Nonofficial Remedies, a distinction between two scarlet red compounds has been made; scarlet red medicinal Biebrich is described as tolylazotolylazobetanaphthol; scarlet red sulfonate is described as the sodium salt of azobenzenedisulfonic acid azobetanaphthol; it differs from the former in that the methyl group (CH<sub>3</sub>—) of the tolyl radicals has been replaced by sodium sulfonate (—SO<sub>3</sub>Na) groups. The name “Biebrich scarlet red, medicinal” which occurs in medical literature, was erroneously applied in the first place; the name Biebrich scarlet is used in dye indexes only for the dye here listed as scarlet red sulfonate.

*Actions and Uses.*—Scarlet red medicinal Biebrich and scarlet red sulfonate have been claimed to have a marked power of stimulating the proliferation of epithelial cells.

Opinions are divided as to the clinical value, but the dyes are used to promote the growth of epithelium in the treatment of burns, wounds, chronic ulcers, etc. In chronic ulcers, however, it is requisite that the local circulation be good in order to obtain a permanent result.

*Dosage.*—The scarlet red preparations are generally used in the form of an ointment containing from 4 to 8 per cent of the substance. The 8 per cent ointment is somewhat irritating and should be alternated with a soothing ointment.

**SCARLET RED-N. F.**—Sudan IV.—Scarlet Red, Medicinal.—Biebrich Scarlet Red.—“An azo dye, *o*-tolyl azo-*o*-tolyl azo- $\beta$ -naphthol.” *N. F.* The structural formula may be represented as follows:



For description and standards see The National Formulary under Scarlet Red and Scarlet Red Ointment.

*Actions, Uses and Dosage.*—See general article, Azo Compounds.

HEILKRAFT MEDICAL COMPANY

**Scarlet Red Salve:** Scarlet red medicinal, 8 parts, eucalyptol, 2 parts, and petrolatum, 90 parts.

MERCK & Co., INC.

**Scarlet Red Medicinal Biebrich (Powder):** bulk.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

**Scarlet Red Biebrich Medicinal (Powder):** bulk.

**SCARLET RED SULFONATE.**—Biebrich Scarlet, water soluble.—The sodium salt of azobenzenedisulfonic acid azobetanaphthol.—The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions, Uses and Dosage.*—See general article, Azo Compounds.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

**Scarlet Red Sulfonate (Powder):** bulk.

PARKE, DAVIS & COMPANY

**Ointment Scarlet Red 5%:** Scarlet red sulfonate, 5 parts; petrolatum containing a small amount of wax, 95 parts.

**Ointment Scarlet Red 10%:** Scarlet red sulfonate, 10 parts; petrolatum containing a small amount of wax, 90 parts.

### *Acridine Derivatives*

The acridine derivatives are mostly yellow dyes—acridine dyes obtained from coal tar—to which the term “flavine” has been applied (“flavine” should more correctly be applied to a vegetable coloring matter). The representative acridine dyes used in medicine are acriflavine hydrochloride (introduced as “trypanflavine” and “acriflavine”), acriflavine base (introduced



as "neutral tryptaflavine" and "neutral acriflavine"), and proflavine. In 1912, Ehrlich found that the acridine dye diaminomethylacridinium chloride hydrochloride possessed therapeutic properties when used in trypanosome infections and hence he termed it *tryptaflavine*. Later this substance was investigated in England, particularly in regard to its effects as a wound antiseptic, and the name "acriflavine" was applied to it. In a generic sense the terms "tryptaflavine" and "acriflavine" have been applied both to acriflavine base and acriflavine hydrochloride. Another closely related substance, diaminoacridine monohydrogen sulfate, was studied also, to which was given the name "proflavine." A considerable number of bacteriologic and clinical reports on these substances have been published. It appears to be established that these dyes possess marked antiseptic and germicidal properties, and on this account they have been employed in a number of pathologic conditions.

*Actions and Uses.*—The antiseptic or bacteriostatic action of acriflavine hydrochloride and proflavine appears to be weakened in the presence of serum. In the treatment of wounds, it is claimed that these drugs are comparatively free from toxic or irritant action on living tissues and that they do not inhibit appreciably the phagocytic action of the leukocytes. Acriflavine hydrochloride is claimed to exert a specific bactericidal action on the gonococcus. The evidence indicates that it has a greater antiseptic action than proflavine, though its action is slower. Applications of acriflavine hydrochloride, acriflavine base and proflavine have been employed in the treatment of wounds, urethritis, gingivitis, gonorrheal conjunctivitis, blenorrrhea, eczema, furunculosis, otitis media, and other conditions requiring the use of a germicide. When taken by mouth, the dyes tend to render the urine antiseptic provided the reaction of the secretion be alkaline. The use of acriflavine base rather than acriflavine hydrochloride has been suggested in areas where freedom from irritation (due to the acid reaction of acriflavine hydrochloride and proflavine) is desirable. The intravenous use of acriflavine base has been proposed, but critical evidence for its necessity is lacking.

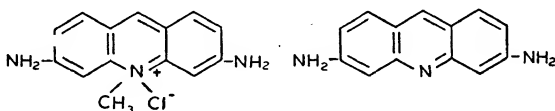
*Dosage.*—In the treatment of wounds, the solution generally employed is 1 in 1,000 in physiological solution of sodium chloride, although weaker solutions may be used. In suppurating wounds, this solution is used for syringing and swabbing the wound after free incision, for irrigation after providing adequate drainage, and for saturating the gauze with which the wound is finally covered. Evaporation should be prevented by protective dressing. In cavities, gauze saturated with the solution may be used as a light packing. Fresh wounds are cleansed thoroughly with the solution, and as much of the solution as possible is left in contact with the injured surfaces. Such wounds may be closed by suture and may be expected to heal by first intention.

In the treatment of open wounds, an ointment has been used

which contains 1 per cent of proflavine oleate (prepared from proflavine base) in an ointment base composed of equal parts of petrolatum and calcium carbonate. A thick layer of the ointment may be spread on gauze and applied to the surface of the cleansed wound, or the ointment may be spread on the wound directly. The primary dressing need not be changed for several days.

In gonorrhea, a strength of 1 in 1,000 in isotonic solution of sodium chloride may be used for injection into the urethra. For irrigation, when relatively large quantities are to be used, a 1 in 4,000 solution is preferable because it is less irritating; solutions of from 1 in 6,000 to 1 in 10,000 have been used. In throat infections a spray of 1 in 1,000 solution is used. In middle ear suppurations a 1 in 500 solution in 50 per cent alcohol is dropped into the ear or the cavity may be packed with gauze wet with the solution. In gingivitis the mouth is irrigated with a 1 in 1,000 solution. Solutions of acriflavine hydrochloride, acriflavine base and proflavine may be boiled, or heated in an autoclave to 130 C., without decomposition, but they are sensitive to light and should be stored in amber bottles. Solutions over a week old should be discarded.

**ACRIFLAVINE-N. F.**—Acriflavine Base.—Neutral Acriflavine.—“A mixture of 2,8-diamino-10-methylacridinium chloride and 2,8-diaminoacridine containing, when dried to constant weight at 100° C., not less than 13.3 per cent and not more than 15.8 per cent of Cl.” *N. F.* The structural formulas of these compounds (which are now properly named 3,6-diamino-10-methylacridinium chloride and 3,6: diaminoacridine) may be represented as follows:



For description and standards see The National Formulary under Acriflavine.

*Actions, Uses and Dosage.*—See general article, Acridine Derivatives.

ABBOTT LABORATORIES

**Acriflavine (Powder):** bulk.

**Enterab Acriflavine:** 30 mg. and 100 mg. Each tablet is enteric coated with a resin prepared from stearic acid, phthalic anhydride and glycerine.

U. S. trademark 353,674.

**Tablets Acriflavine:** 0.1 Gm. One tablet dissolved in 100 cc. of isotonic solution of sodium chloride makes a 1:1,000 solution.

**Tablets Acriflavine:** 30 mg. One tablet dissolved in 30 cc. of isotonic salt solution makes a 1:1,000 solution.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

**Acriflavine (Neutral) (Powder):** bulk.

**Acriflavine "Pro Injectione" (Neutral):** 0.5 Gm. and 1.0 Gm. vials.

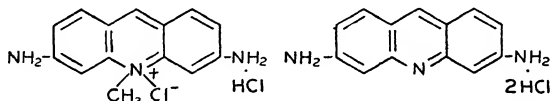
**Ointment Acriflavine (Neutral), 1%:** Acriflavine, 1 part, dissolved in glycerin, 8 parts, and incorporated with a base composed of hydrous wool fat and petrolatum to make 100 parts.

**Tablets Acriflavine (Neutral):** 0.1 Gm.

**Enteric Coated Tablets Acriflavine (Neutral):** 32.4 mg. Each tablet is coated with phenyl salicylate containing some keratin.

**Troches Acriflavine (Neutral):** Each troche contains neutral acriflavine, 6 mg.; menthol, 0.6 mg. and sodium chloride, 0.6 mg.

**ACRIFLAVINE HYDROCHLORIDE-N. F.**—"A mixture of the hydrochlorides of 2,8-diamino-10-methylacridinium chloride and 2,8-diaminoacridine containing when dried to constant weight over sulfuric acid, not less than 23 per cent and not more than 24.5 per cent of Cl." *N. F.* The structural formulas of these compounds (which more properly are name 3,6-diamino-10-methylacridinium chloride and 3,6-diamino acridine) may be represented respectively, as follows:



For description and standards see The National Formulary under Acriflavine Hydrochloride.

**Actions, Uses and Dosage.**—See general statement on Acridine Derivatives.

ABBOTT LABORATORIES

**Acriflavine Hydrochloride (Powder):** bulk.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

**Acriflavine Hydrochloride (Powder):** bulk. Controlled biologically so that the maximum nonlethal dose for mice weighing 20 Gm. shall not exceed 15 mg.

To determine the maximum nonlethal dose the drug is dissolved in water in such concentration that 1 cc. contains the quantity to be administered. A series of mice weighing 20 Gm. each are injected subcutaneously with small doses of the drug, each succeeding animal receiving an increase of  $\frac{1}{10}$  mg. of the drug over the preceding one. The dosage under which all of the animals survive and over which all die is the maximum nonlethal dose.

**DYMIXAL-McNeil**—A mixture of three dyes containing crystal violet 46 per cent, brilliant green 31 per cent and acriflavine 23 per cent. It may be prepared by mechanical mixing of the three dyes in their solid state.

For tests and standards, see Section B.

*Actions and Uses.*—This mixture is proposed for the treatment of burns. It possesses antiseptic action and forms a flexible eschar. It appears to be more advantageous than a single dye in antiseptic effect against gram-positive and gram-negative bacteria.

*Dosage.*—Dymixal may be applied directly to the wound as a jelly or as a 2.6 per cent aqueous solution. If an oily substance has been used it should be removed before dymixal is applied. Blebs should be excised and loose pieces of skin removed. When the solution is applied, a new application can be made as fast as each one dries, the usual procedure requiring about six applications. The jelly may also be applied in several applications, being spread thinly during each application.

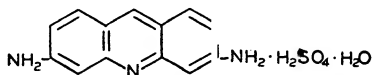
#### MCNEIL LABORATORIES

**Dymixal (Powder):** 6.5 Gm. and 65 Gm. bottles.

**Dymixal Jelly 2%:** 56.7 Gm. collapsible tubes. A water soluble jelly containing dymixal 2 per cent, glycerin 5 per cent, methyl cellulose 5 per cent and water.

U. S. trademark 378,611.

**PROFLAVINE SULFATE-N. F.**—Proflavine.—3,6-Diaminoacridinium monohydrogen sulfate. The structural formula may be represented as follows:



For description and standards see The National Formulary under Proflavine Sulfate.

*Actions, Uses and Dosage.*—See general article, Acridine Derivatives.

#### NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

**Proflavine (Powder):** bulk. Controlled biologically so that the maximum nonlethal dose for mice weighing 20 Gm. does not exceed 6 mg.

### **Triphenylmethane (Rosaniline) Derivatives**

Of the derivatives of triphenylmethane and its homologue tolyldiphenylmethane, the most interesting medicinally are those which result from the introduction of amino groups forming pararosaniline (triaminotriphenylcarbinol  $(\text{NH}_2\text{C}_6\text{H}_4)_3\text{COH}$ ) and rosaniline (triaminotriphenyltolylcarbinol  $(\text{NH}_2\text{C}_6\text{H}_4)_2(\text{CH}_3.\text{NH}_2\text{C}_6\text{H}_3).\text{COH}$ ). On treating rosaniline with hydrochloric acid, the hydroxyl of the carbinol group is split off, permitting the formation of a quinoid group; thus is formed a typical dye known as fuchsin,  $\text{NH}_2\text{C}_6\text{H}_4.\text{CH}=\text{N}.\text{NH}_2\text{C}_6\text{H}_3:\text{C}=\text{C}_6\text{H}_4.\text{NH}_2\text{Cl}$ . The red color of pararosaniline chloride or fuchsin is changed to violet as methyl groups are substituted for the hydrogens in the amino groups. The intensity of the violet color is augmented in direct proportion to the increase in the number of methyl groups. There are three closely related triphenylmethan derivatives, namely gentian violet, crystal violet and methyl violet. Gentian violet is hemamethylpararosaniline chloride with an admixture, usually of pentamethylpararosaniline and tetramethylpararosaniline chlorides; by some it is defined as a mixture of methyl violet and crystal violet. Crystal violet is a relatively pure form of hexamethylpararosaniline chloride; methyl violet is considered to contain mostly pentamethylpararosaniline chloride with some of the hexaderivative and probably some tetraderivative also. Hence, one definition of gentian violet is practically the same as the other. It seems likely that in therapeutics it will be found that there is little difference between the penta and hexa derivatives and the mixtures of the two, so that the one most easily obtained in pure form (crystal violet) will be the one most used. The material which has been used by the workers so far, however, has been gentian violet.

Gentian violet was introduced as an antiseptic by J. Stelling in 1890 and has been advocated by Churchman, who found that solutions of the dye had a selective action on certain bacteria and that the majority of gram-negative organisms survived exposure to gentian violet solutions in strengths far in excess of that required to kill gram-positive organisms; in fact, the action of the dye is sufficiently selective, so that often a "strain within a species" is not affected. Churchman's work, however, was done largely with a product containing dextrin as a diluent. Churchman also has found that acid fuchsin (the acid sodium salt of fuchsin disulfonic and trisulfonic acids) is in some respects the opposite of that of gentian violet in selective power, a stained culture of *Ser. marcescens* (*prodigiosus*) being killed by the acid fuchsin, while the gram positive *B. anthracis* would be unaffected. The selective action of acid fuchsin, however, is clearly brought out only when the organisms are exposed to the dye with slight elevation of temperature (about 50 C.). Acid fuchsin is incompatible with gentian violet, and the compatibility of all mixtures of dyes should be determined before any combination is prepared. Churchman claimed, however, that acriflavine possesses much the same selectivity as acid fuchsin, so he proposed the use

of a mixture of these two dyes. The effectiveness of such a solution has not yet been established clinically. Aldrich [New England J. Med. 217: 911 (Dec. 2) 1937] has proposed a triple-dye-mixture of gentian violet 3 parts, brilliant green 2 parts, neutral acriflavine 1 part by weight, 2 Gm. of which is dissolved in 100 cc. of water to make a solution for spraying burns that is reported to produce a suitable eschar and reduce infection. None of the rosaniline dyes is a strong bactericide.

Rosaniline dyes are also employed for the treatment of superficial fungus infections of the skin. Fuchsin, the dye component of Castellani's paint is widely employed for this purpose, as are also gentian violet and the acridine dye, acriflavine. Their principal disadvantage is the staining of clothing that may occur with their use.

**CARBOL-FUCHSIN PAINT.** — *Carfusin-Rorer.* — A solution containing boric acid 1%, phenol 4.5%, resorcinol 10%, fuchsin 0.3%, acetone 5% and alcohol 10% in water, q. s.

The boric acid, phenol, resorcinol, fuchsin and acetone used in the preparation of this particular preparation meet the requirements of the U. S. Pharmacopeia or The National Formulary.

*Actions and Uses.* — Carbol-Fuchsin paint is a stabilized preparation of the original basic fuchsin formula known as Castellani's paint that is widely employed for topical application to superficial fungus infections of the skin. Its use should be restricted to subacute or chronic dermatophytoses; it has been found to be of value for epidermophytosis interdigitalis pedum ("athlete's foot"), other intertriginous lesions of fungus origin, tinea trichophytina (ringworm) and tinea imbricata.

Carbol-fuchsin paint has the advantage over the original and subsequently modified preparations in that it is stable, but it should be protected against evaporation. It shares with other triphenylmethane dyes the disadvantage that it will stain clothing with which it comes in contact. It should never be applied to large areas of the body or to patients with particularly sensitive skins. A test application of a 1:3 dilution should be made to a single small lesion before beginning treatment with the full strength paint. It should be properly guarded against accidental ingestion because of the poisonous character of the ingredients.

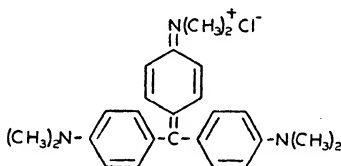
*Dosage.* — Carbol-fuchsin paint is applied full strength directly to the surface of the skin lesions. Thorough topical application once or twice daily is indicated in subacute phases; three times daily in chronic or particularly stubborn lesions. Interim use of a foot powder and twice daily change of hosiery is recommended in the treatment of epidermophytosis pedis. In cases associated with excessive drying of the skin, application of the paint may be continued in conjunction with applications of either boric acid ointment containing 2 to 5 per cent of ammoniated mercury or an ointment of petrolatum containing 1 per cent each of sulfur and salicylic acid and 25 per cent each of zinc oxide and talc.

WILLIAM H. RORER, INC.

**Carfusin:** 30 cc. and 120 cc. bottles. A solution of boric acid 1%, phenol 4.5%, resorcinol 10%, fuchsin 0.3%, acetone 5% and alcohol 10% in water, q. s.

U. S. trademark applied for.

**METHYLROSANILINE CHLORIDE U. S. P.**—Gentian Violet, Methyl Violet, Crystal Violet.—“Hexamethylparosaniline usually admixed with pentamethylparosaniline chloride and tetramethylparosaniline.”—U. S. P. The structural formula of hexamethyl-*p*-rosaniline may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Methylrosaniline Chloride and The National Formulary under Methylrosaniline Chloride Jelly and Methylrosaniline Chloride Solution.

**Actions and Uses.**—Methylrosaniline chloride is a useful antiseptic for infected wounds, mucous membranes and serous surfaces. Its chief application has been in the treatment of affections of the pleural cavity and of the joints, particularly in empyema and arthritis—affections in which staphylococci *Ps. aeruginosa* and *C. diphtheriae* are the causative agents. Evidence has been advanced that methylrosaniline chloride, administered in enteric coated tablets, is of value as an anthelmintic in the treatment of *Strongyloides* infestation.

**Dosage.**—60 mg. U. S. P. For direct application, a solution of from 1 in 500 to 1 in 1,000 may be employed; for instillation, a 1 in 10,000 solution.

THE COLEMAN & BELL COMPANY, INC.

**Gentian Violet Improved Medicinal (Powder):** bulk Gentian violet medicinal.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

**Gentian Violet Medicinal (Powder):** bulk.

**Tablets Gentian Violet Medicinal:** 32.4 mg.

**Enteric Coated Tablets Gentian Violet Medicinal:** 32.4 mg. The tablets are coated with phenyl salicylate containing some keratin.

## Formaldehyde

The antiseptic actions of formaldehyde cannot be utilized directly on the body because of the irritant and coagulant effects. Attempts have been made to avoid these effects by combining the formaldehyde in such a way as to cause it to be liberated very gradually. The results have been rather disappointing, because it is difficult, if not impossible, to secure just that degree of stability in which the formaldehyde will be liberated in concentrations sufficient to maintain the antiseptic action, but not sufficient to become irritant. Methenamine (hexamethylenetetramine) is a notable exception; but its effects are confined to acid fluids, and, therefore, essentially to the urine. Other compounds are effective mainly through the other constituents with which the formaldehyde is combined, rather than through the formaldehyde itself.

The wide reactivity of formaldehyde gives the possibility of a great variety of compounds; with proteins; carbohydrates; amides; phenols and aromatic derivatives. Methenamine does not contain formaldehyde as such, but liberates it under certain conditions (See systemic anti-infectives).

**FORMALDEHYDE SOLUTION-U. S. P.**—Formalin.—“A solution containing not less than 37 per cent of HCHO with variable amounts of methanol to prevent polymerization.” *U. S. P.* The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Formaldehyde Solution.

*Actions, Uses and Dosage.*—Formaldehyde solution is germicidal in the strength of from 1 to 2 per cent (percentages refer to amounts of absolute formaldehyde, HCHO), but the action may be delayed from 20 to 30 minutes. In the concentration of 1 in 5,000, it restrains the growth of many organisms, and in many cases a strength of 1 in 20,000 or 1 in 30,000 is sufficient to prevent the multiplication of bacteria. Formaldehyde solution 1 per cent is suitable for disinfection of shoes contaminated from fungus infections of the feet, after preliminary washing with soap solution. All traces of formaldehyde can be neutralized in a bath of 0.5 per cent sodium bisulfite. It hardens tissues and is used in histology for this purpose. It has a similar hardening effect on the living skin; it is very irritating and produces reddening, inflammation and necrosis if applied repeatedly or continuously. Solutions of 1 to 10 per cent in alcohol are applied to the skin to prevent excessive sweating. It is sometimes used with a solution of soap for the disinfection of the hands.



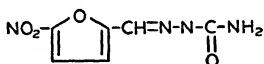
It is also employed for the preparation of toxoids. The use of formaldehyde for the preservation of food is condemned.

MERCK & Co., INC.

**Solution of Formaldehyde:** bulk.

### Furan Derivatives

**NITROFURAZONE.**—Furacin-Eaton Labs.—5-nitro-2-furaldehyde semicarbazone.— $C_6H_6O_4N_4$ .—M. W. 198.15. A synthetic antibacterial substance derived from furfural, possessing the following structural formula:



For tests and standards, see Section B.

**Actions and Uses.**—Nitrofurazone is a substituted furan compound possessing bacteriostatic and bactericidal properties; it is inhibitory in broth with concentrations of 1:100,000 to 1:200,000 and bactericidal at 1:50,000 to 1:75,000. It is not soluble in much less than 5,000 parts of water. It is effective in vitro and in vivo against a variety of gram negative and gram positive bacteria; it has least bacteriostatic activity against *Bacillus pyocyaneus* and little bactericidal effect on *Diplococcus pneumoniae*.

Nitrofurazone is useful for topical application in the prophylaxis and treatment of superficial mixed infections common to contaminated wounds, burns, ulceration and certain diseases of the skin. It may be useful as an adjunct to surgery in the preparation of areas for skin grafting and in the treatment of osteomyelitis. Daily application for periods of one month or longer may produce a local reaction in a small percentage of cases. Sensitivity or intolerance to its local use has been observed and may be cause for its discontinuance. Continuous applications for periods as long as five days may be capable of producing sensitization and a generalized allergic skin reaction. Photosensitization from sunlight has not been encountered. Variant bacterial strains showing induced resistance to sulfathiazole, penicillin or streptomycin are as susceptible to nitrofurazone as their parent strains. Induced resistance to the aforementioned agents does not entail resistance to nitrofurazone.

Systemic toxicity due to absorption of the compound is considered unlikely. Clinical studies indicate that the ingestion of 1 to 3 Gm. daily for long periods is fairly well tolerated by the majority of human subjects, but until more conclusive evidence of its mode of action and chemotherapeutic value becomes available its internal use cannot be recommended.

**Dosage.**—Nitrofurazone is used topically in an ointment-like base containing a concentration of 1:500 (0.2 per cent). It is

applied locally either directly or to dressings that cover the infected area. The base is water soluble but liquefies at body temperature and may thus require special coverings to maintain effective contact with certain areas to which it may be applied. Dressings may be reinforced with cellophane or similar material, and petrolatum gauze may be used for a barrier to limit the absorption into the dressing. On exposure to light, the bright yellow nitrofurazone turns dark brown. This is not associated with any ill effects and may be avoided by covering with light dressings.

#### **EATON LABORATORIES, INC.**

**Furacin Soluble Dressing 1:500:** 113 Gm. and 454 Gm. jars. Each hundred grams contains Furacin 0.2 Gm., Carbowax (1540) 30 Gm., Carbowax (4000) 15 Gm. and polyethylene glycol (300) 54.8 Gm.

**Solution Furacin 1:500:** 473 cc. bottles. Each 100 cc. contains nitrofurazone 0.2 Gm. and polyethylene glycol of mono-iso-octyl phenyl ether 0.3 Gm. in a mixture of polyethylene glycol 300, 32.5 Gm.; "carbowax 1540," 32.5 Gm., and water.

U. S. patent 2,319,481 (expires 1962); 2,416,234 (expires 1964); U. S. trademark 403,279.

## **Halogen Compounds**

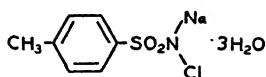
### ***Chlorine Derivatives***

The germicidal action of free chlorine and the hypochlorites is well known. In medicine this action has been utilized by the employment of chlorine water, chlorinated lime and alkaline solutions of sodium hypochlorite (Labarraque's solution), and potassium hypochlorite (Javelle water).

Hypochlorite preparations are fairly stable in the presence of alkali, and alkaline hypochlorite preparations have the added advantage that the alkali has a destructive and solvent action on most bacteria and other organic matter. In the treatment of infected wounds with hypochlorite solutions, an excessive degree of alkalinity is held to be objectionable on the grounds that it causes destruction of normal tissue and irritation of the skin.

On the theory that the action of hypochlorites is dependent on the combination of their active chlorine ( $\text{Cl}^+$ ) with the nitrogen of protein, certain organic preparations containing a chloramid group, which are practically neutral and relatively stable, have been proposed as substitutes.

**CHLORAMINE-T—N.F.—Chlorazene-Abbott.** — Chloramine. — Sodium *p*-Toluene-sulfonchloroamide. — "Chloramine-T more than 13 per cent of active  $\text{Cl}^+$ ." — *N. F.* The structural formula may be represented as follows:



For description and standards see The National Formulary under Chloramine-T.

**Actions and Uses.**—The actions of chloramine-T are essentially similar to those of diluted sodium hypochlorite solution.—N. F. It has the advantages of greater stability, convenience of preparation, and the production of less irritation. On the other hand, it lacks the solvent action of alkaline hypochlorites.

It is practically nontoxic, but should not be used by mouth, since it is decomposed by the gastric juice.

**Dosage.**—Chloramine-T is used in 0.1 to 4 per cent aqueous solution. For wounds, the normal strength is from 1 to 2 per cent, applied by the same technic as the surgical solution of chlorinated soda. It has also been employed for irrigation of the urethra, bladder and uterus, and as a mouth wash.

#### ABBOTT LABORATORIES

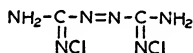
**Chlorazene (Powder):** 37.8 Gm., 56 Gm., 113 Gm. and 189 Gm. bottles. Chloramine-T.

**Aromatic Chlorazene (Powder):** 454 Gm. and 2.27 Kg. bottles. Chloramine-T, 5 per cent; sodium bicarbonate, 5 per cent; eucalyptol, 2 per cent; saccharin, 1 per cent; sodium chloride, 87 per cent.

**Tablets Chlorazene:** 0.3 Gm.

U. S. trademark 119,014.

**CHLOROAZODIN-U. S. P. — Azochloramid-Wallace & Tiernan.**—"Contains the equivalent of not less than 37.5 per cent and not more than 39.5 per cent of active chlorine (Cl)."—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Chloroazodin and Solution of Chloroazodin.

**Actions and Uses.**—Similar to those of a dilute solution of sodium hypochlorite, chloramine-T and of dichloramine-T except that it does not hydrolyze appreciably in aqueous solutions and that its rate of reaction with mild reducing agents and organic matter in general is low. Consequently, its concentration does not decrease rapidly and it is claimed that it exerts a more prolonged and stronger bactericidal action in the presence of tissue fluids and exudate than the other chloramines.

Solutions of chloroazodin are used on dressings for wounds and on packings for infected cavities. Aqueous solutions are suitable for lavage of wounds, and for irrigations of and instillations into cavities. It is claimed that short exposure of epithelial tissue to aqueous solutions is harmless and that solutions of chloroazodin in vegetable oil (1:2,000) are applicable to the mucous membrane of the vagina, colon, and rectum. The available evidence indicates that chloroazodin possesses relatively low toxicity and is a relatively nonselective bactericidal agent.

*Dosage.*—Chloroazodin is usually employed in wounds in a dilution of 1:3,300 in an approximately isotonic solution buffered at pH 7.4. Greater dilutions up to 13,200 are proposed for use on mucous membranes. On dressings and packings the stable solution containing 1 part of chloroazodin in 500 parts of glyceryl triacetate (triacetin) is used. Gauze impregnated with the triacetin solution of chloroazodin does not dry out and does not stick to the wound. A solution prepared by mixing one volume of a strong solution of chloroazodin in triacetin (1:125) with 19 volumes of a vegetable oil contains one part of chloroazodin in 2,000 parts (by weight) of the solution and is claimed to be sufficiently bland to be applicable to certain mucous membranes.

WALLACE & TIERNAN PRODUCTS, INC.

**Saline Mixture of Azochloramid (Powder):** This contains chloroazodin 3.17 per cent, sodium chloride 89.56 per cent, monopotassium phosphate 0.95 per cent, and sodium phosphate exsicc. 6.32 per cent by weight. Bottles of the powder containing 35.93 Gm. for preparing 1 gallon and bottles of the powder containing 1,800 Gm. for preparing 50 gallons of aqueous solution of Azochloramid (1:3,300).

**Surface Active Saline Mixture of Azochloramid (Powder):** 4.7 Gm. envelopes and 37.85 Gm. bottles. A mixture containing Azochloramid 3.1 per cent, sodium tetradecyl sulfate 10.0 per cent, sodium chloride 80.7 per cent, monopotassium phosphate 0.8 per cent and anhydrous sodium phosphate 5.4 per cent. The 4.7 Gm. envelopes and the 37.85 Gm. bottles are used for the preparation of 1 pt. and 1 gal., respectively, of a surface active solution of Azochloramid, 1:3,300.

**Solution of Azochloramid in Triacetin (1:500).**—A solution containing chloroazodin 1 Gm. in 500 Gm. of triacetin. Triacetin is a mixture of glyceryl acetates containing approximately 95 per cent of glyceryl triacetate.

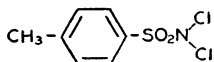
U. S. patent 2,073,256 (March 8, 1937; expires 1954).

**Strong Solution of Azochloramid in Triacetin (1:125).**—A solution containing chloroazodin 1 Gm. in 125 Gm. of triacetin for use in the preparation of Azochloramid in vegetable oil (1:2,000).

**Tablets Saline Mixture of Azochloramid.** Each tablet contains 0.55 Gm. of the Saline Mixture of Azochloramid for preparing 60 cc. of the aqueous solution of Azochloramid (1:3,300).

U. S. patent 1,958,370 (March 8, 1934; expires 1951). U. S. trademark 322,242.

**DICHLORAMINE-T — N.F.** — *p*-Toluenesulfondichloroamide.—Dichloramine.—“Dichloramine-T contains the equivalent of not less than 28 per cent and not more than 30 per cent of active Cl.” *N. F.*



For description and standards see The National Formulary under Dichloramine-T.

**Actions and Uses.**—Dichloramine-T is an effective germicide through its content of active chlorine (Cl+). It is only sparingly soluble in water, but soluble in chlorinated eucalyptol or chlorinated paraffin (chlorcosane). The solution produces a gradual, sustained antiseptic action.

It is more irritant than chloramine, but also more solvent. It should not be administered internally.

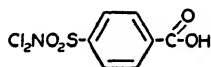
Dichloramine-T is claimed to be useful in the prevention and treatment of diseases of the nose and throat; it has been used with success when applied to wounds.

**Dosage.**—Dichloramine-T dissolved in chlorinated paraffin (which see) is used in concentrations of from 0.5 to 10 per cent. In nasopharyngeal work from a 1 to a 2 per cent solution is employed; for application to wounds a 5 per cent solution. The solution of dichloramine-T in chlorinated paraffin is not very stable and should not be kept for more than two or three days. At times the solutions may become irritating to the skin because of the formation of hydrochloric acid. Both dichloramine-T powder and solution should be protected from sunlight to prevent decomposition.

ABBOTT LABORATORIES

**Dichloramine-T (Powder):** bulk.

**HALAZONE-N.F.** — *p*-sulfonedichloramidobenzoic Acid.— $\text{C}_6\text{H}_4(\text{SO}_2\text{NCl}_2)\text{COOH}$ —1:4.—“Contains the equivalent of not less than 24 per cent and not more than 26.26 per cent of active Cl.”—*N. F.* The structural formula may be represented as follows:



For description and standards see The National Formulary under Halazone.

**Actions and Uses.**—Halazone is said to be a powerful disin-

fectant. It is said to act like chlorine, but to have the advantage of being stable in solid form. In the presence of alkali carbonate, borate and phosphate, Dakin and Dunham report that, in from thirty to sixty minutes, halazone in the proportion of from 1 in 200,000 to 1 in 500,000 sterilized polluted water contaminated with such organisms as *Bacterium coli*, *Bacterium typhosum*, *Bacterium paratyphosum* A and B, *Vibrio cholerae* and *Bacterium dysenteriae*.

**Dosage.**—For the sterilization of water, 4 to 8 mg. of halazone, in the form of tablets containing sodium carbonate (or sodium borate) and sodium chloride, is added to 1 liter.

ABBOTT LABORATORIES

**Halazone (Powder):** bulk.

**Tablets Halazone:** Halazone, 4 mg., sodium borate, 11 mg. and sodium chloride sufficient to make about 0.13 Gm.

**SODIUM HYPOCHLORITE SOLUTION—Hyclorite-Pennsylvania Salt Co.**—A solution of chlorinated soda, each 100 Gm. of which is stated to contain sodium hypochlorite 4.05 Gm., sodium chloride 2.50 Gm., calcium hydroxide 0.14 Gm., available chlorine.

For tests and standards, see Section B.

**Actions and Uses.**—Sodium hypochlorite solution differs from Diluted Sodium Hypochlorite Solution-N. F., chiefly by its greater amount of available chlorine and lower alkalinity. It has the actions and uses of other compounds containing sodium hypochlorite. (See the general article, Chlorine Derivatives.) One volume of sodium hypochlorite solution diluted with seven volumes of water has the same available chlorine content (0.43 to 0.48 per cent) as surgical Solution of Chlorinated Soda-U. S. P. X, and is isotonic.

**Dosage.**—Sodium hypochlorite solution is used full strength or diluted with 1 or 2 parts of water for direct application to mucous membrane, muscular tissue, bone infections, etc. For irrigation of wounds, throat and body cavities, dilutions of from 1 in 200 to 1 in 2,000 are used. For use in the irrigation method of treating infected wounds, dilute one part of sodium hypochlorite solution with seven parts of water.

The available chlorine content of sodium hypochlorite solution decreases at the rate of about 12 per cent per year. In order that due allowance for this decrease may be made when diluting for use, each bottle of sodium hypochlorite solution bears the date of bottling.

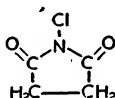
PENNSYLVANIA SALT MANUFACTURING CO.

(Bethlehem Laboratories, Inc., Distributor.)

**Solution Hyclorite:** bulk.

U. S. trademark 120,110.

**SUCCINCHLORIMIDE-N. F.**—N-Chlorosuccinimide.—The chlorinated imide of succinic acid.—“Succinchlorimide contains not less than 25 per cent nor more than 27 per cent of active Cl.”—*N. F.* The structural formula may be represented as follows:



For description and standards see The National Formulary under Succinchlorimide and Succinchlorimide Tablets.

**Actions and Uses.**—Succinchlorimide is proposed for use in disinfection of water. Experiments indicate that succinchlorimide will disinfect water containing *Escherichia coli*, *Eberthella typhi*, *Salmonella paratyphi* A and B, *Vibrio cholerae* and *Shigella dysenteriae* within 20 minutes in dilution of 11.6 parts per million (approximately 1:100,000).

**Dosage.**—For the disinfection of water, 11.6 mg. of succinchlorimide per liter.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORP.

**Succinchlorimide (Powder):** Bulk.

### *Iodine and Iodine Derivatives*

Certain iodine compounds are used for their local irritant and antiseptic effects, which are due probably to the action of free iodine contained in the preparations or liberated from them; or they may be administered for their systemic actions and for roentgen-ray diagnosis.

#### **Iodine Preparations Containing Free Iodine**

**IOCAMFEN**—Schering & Glatz, Division of Wm. R. Warner & Co., Inc. —A liquid obtained by the interaction of iodine 10 parts, phenol 20 parts and camphor 70 parts, containing about 7.25 per cent free iodine.

For tests and standards, see Section B.

**Actions and Uses.**—Iocamfen has the antiseptic and germicidal properties of iodine and the analgesic and stimulating properties of camphor and phenol.

Iocamfen is used especially in the treatment and dressing of wounds, and in dentistry; also in ringworm of the feet, nails, and other parts of the body.

**Dosage.**—Iocamfen is applied in small quantities directly to wounds, the skin, cavities, etc., or on tampons or drainage material.

SCHERING & GLATZ, DIVISION OF WM. R. WARNER & CO., INC.

**Iocamfen (Liquid):** 30 Gm. and 113 Gm. bottles.

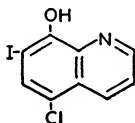
U. S. trademark 112,934.

### Iodine Dusting Powders

Dusting powders containing iodine in various combinations are used in the treatment of wounds, granulating surfaces, abscess cavities, etc. The clinical results are ascribed to a slight antiseptic action of the iodine, to stimulation of phagocytosis, and to diminished secretion from the wound which renders it a less favorable culture medium for germs.

Iodoform has been the standard drug of this class. Other insoluble organic iodine compounds have been introduced to replace iodoform, but with limited success. While they avoid the disagreeable odor and the occasional toxic systemic effects, they also lack much of the efficiency.

**ODOCHLOROXYDROXYQUINOLINE-N. F.—Vioform-Ciba.**—5-chloro-7-iodo-8-hydroxyquinoline. — “Contains not less than 38 per cent and not more than 41.5 per cent of I, and not less than 11.4 per cent and not more than 12.2 per cent of Cl.”—*N. F.* The structural formula may be represented as follows:



For description and standards see The National Formulary under Iodochlorohydroxyquinoline and Iodochlorohydroxyquinoline Tablets.

*Actions and Uses.*—Iodochlorohydroxyquinoline is used as an almost odorless substitute for iodoform; it is also employed against trichomonas vaginitis and, internally, against amebiasis. It is used in atopic dermatitis, eczema of the external auditory canal, eczema of the legs, scalp, scrotum and perineum, also in chronic dermatitis, oil dermatitis, acute psoriasis and intertriginous psoriasis.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endameba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa; positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases. In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes re-examinations and repetitions of courses of treatment.

*Dosage.*—Against amebiasis, 0.75 Gm. to 1.0 Gm. daily (in capsules in divided doses of 0.25 Gm. by mouth for 10 days, with repetition of the course after a rest period of a week to ten



days). A few cases of gastro-intestinal irritation with this dosage have been reported; on account of the high iodine content the possibility of iodism should be kept in mind. Until more evidence becomes available, iodochlorohydroxyquinoline should be used with caution in cases with liver damage. It is used as a dusting powder for application to wounds, ulcers, burns, exudative skin eruptions, etc. It is also used externally as a 2 per cent to 3 per cent ointment, lotion or paste.

*Caution*—Iodochlorohydroxyquinoline used locally stains linen yellow on contact.

CIBA PHARMACEUTICAL PRODUCTS, INC.

**Vioform (Powder):** bulk.

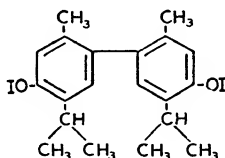
**Vioform Insufflate:** 30 Gm. and 248.8 Gm. bottles containing vioform 25 per cent, boric acid 10 per cent, zinc stearate 20 per cent, lactic acid  $2\frac{1}{2}$  per cent and lactose  $42\frac{1}{2}$  per cent.

**Tablets Vioform:** 250 mg.

**Vioform Vaginal Inserts:** Each insert contains vioform 250 mg., lactic acid 25 mg., boric acid 100 mg. and diluent to make 2 Gm.

U. S. patent 641,491 (Jan. 16, 1900; expired). U. S. trademark 92,732.

**THYMOL IODIDE-N.F.—Aristol-Winthrop-Stearns.**—“A mixture of iodine derivatives of thymol, principally dithymoldiiodide,  $(C_8H_2.CH_3.C_3H_7.OI)_2$ , containing, when dried over sulfuric acid for 18 hours, not less than 43 per cent of I.” *N. F.* The structural formula may be represented as follows:



For description and standards see The National Formulary under Thymol Iodide.

*Actions and Uses.*—Antiseptic, used chiefly as a dusting powder.

MERCK & Co., INC.

**Thymol Iodide (Powder):** bulk.

WINTHROP-STEARNES, INC.

**Aristol (Powder):** Thymol iodide, 30 Gm. bottle.

U. S. trademark 17,393.

## Isoparaffinic Acids

**COPARAFFINATE**—**Iso-Par-Medical Chem.**—A mixture of water insoluble isoparaffinic acids partially neutralized with *isoocetyl* hydroxybenzyl-dialiphatic amines. The water insoluble isoparaffinic acids are obtained by oxidation of petroleum hydrocarbons by the passage of a current of oxygen under pressure at an elevated temperature in the presence of a metallic catalyst. The water insoluble monocarboxylic and dicarboxylic acids with from 6 to 16 carbon atoms are separated and purified by fractional distillation. The hydroxybenzyl-dialiphatic amines are combined directly with the isoparaffinic acids or in a suitable solvent. The latter is then removed by distillation.

For tests and standards, see Section B.

**Actions and Uses.**—Coparaffinate ointment is for external use only. It should not be covered with thick tight bandaging, since irritation may result from this type of dressing. It is said to be of value in the treatment of pruritus ani and vaginae, mycotic infections of the hand and feet and eczemas of the ear and certain skin allergic manifestations. This ointment is stimulating, lowers the levels of irritability of the skin and is in varying degrees bactericidal and fungicidal.

**Dosage.**—It should be applied with a rubber finger stall, a small wad of absorbent cotton or gauze, or other convenient applicator, since it possesses an odor which may be objectionable if it persists on the fingers. The first applications may cause a temporary burning sensation, but this disappears later. The ointment should be applied to the affected area in the evening before retiring and again in the morning; if necessary, it may be applied more frequently. It is claimed that the majority of cases will show evidence of response within three to five days, possibly up to two weeks. If by that time relief is not obtained, some other form of treatment should be substituted.

MEDICAL CHEMICALS, INC.

**Ointment Iso-Par Coparaffinate:** 14 Gm., 28.5 Gm., 114 Gm. and 454 Gm. jars. Contains Iso-Par 17 per cent and titanium dioxide 4 per cent in an ointment base consisting of beeswax, cetyl alcohol, lanolin and petrolatum.

U. S. patent 2,262,720 (expires 1958). U. S. trademark 365,069.

## Metal Compounds

### *Bismuth*

The insoluble compounds of bismuth are used for their mechanical action as protectives of inflamed or irritated surfaces. On a wound, a firm crust is formed, beneath which healing proceeds. The drying property of the powder is of chief importance, and the antiseptic action secondary. For the best development of the protective mechanical action, a very finely divided

bismuth compound is essential. This fine division has been secured in various ways. The powder is given alone or prepared in a permanent suspension holding the bismuth in such a fine state of division as to favor its deposition evenly throughout the whole intestinal tract. Soluble complex salts of bismuth, which are decomposed by dilute mineral acids with precipitation of insoluble bismuth salts in a very fine state of subdivision, are administered with the expectation that the gastric juice will bring about precipitation and thus protect the digestive tract. It is questionable whether this assumption is realized in many cases. Pharmacologists and many clinicians doubt the usefulness of all soluble bismuth preparations as a means of securing their protective action.

Bismuth has been combined with other substances, either in mixture or in synthetic compounds, to produce insoluble compounds easily administered or of enhanced protective and antiseptic actions. It is doubtful whether combination with antiseptic acids, as in bismuth subgallate or bismuth subsalicylate, increases the efficiency of the preparation. The antiseptic acids lose their power in alkaline liquids, as in the intestines; the introduction of iodine into the benzene nucleus does not increase the antiseptic power. On the other hand, bismuth compounds with phenol or with phenols in which bromine or iodine has replaced hydrogen in the benzene ring have an antiputrefactive action.

Soluble compounds of bismuth used for their protective action should be employed with caution because of the danger of absorption of poisonous amounts of bismuth. Absorption of insoluble bismuth compounds from wounds and cavities occasionally occurs. Skin lesions similar to those sometimes following the use of arsphenamine are among the most important complications of bismuth therapy. For example, a pruritus, an erythema, an urticaria or a dermatitis, and rarely hemorrhagic lesions, are noted following bismuth therapy; and cases of agranulocytosis with angina have been reported. The administration of the drug should be stopped on the first sign of cutaneous irritation. Bismuth poisoning is indicated by a blue line on the gums, and by stomatitis. In some patients undergoing bismuth therapy systemic symptoms of malaise, nausea, headaches and vague rheumatic muscular and bone pains have been noted. Removal of the bismuth therapy is the principal treatment. Too free local application of bismuth-containing powders or too free injection into cavities should be avoided. Large doses of bismuth subnitrate have produced nitrite poisoning by its reduction in the colon.

**BISMUTH SUBNITRATE-N. F.**—Basic Bismuth Nitrate.—“A basic salt which, when dried over sulfuric acid for 18 hours, yields upon ignition not less than 79 per cent  $\text{Bi}_2\text{O}_3$  [bismuth oxide].”—*N. F.*

For description and standards see The National Formulary under Bismuth Subnitrate and Bismuth Subnitrate Tablets.

PARKE, DAVIS & COMPANY

**Bismuth Paste Surgical:** Bismuth subnitrate, one part, in yellow petrolatum, two parts.

**BISMUTH TRIBROMOPHENATE.** — Xeroform-Schering & Glatz, Division of Wm. R. Warner & Co., Inc. — A basic bismuth tribromophenate of variable composition.

For tests and standards, see Section B.

*Actions and Uses.*—Bismuth tribromophenate is claimed to be a nonirritating and nontoxic antiseptic. Occasionally cases of sensitization to its local use are noted. It is said to be valuable in ulcers cruris, in impetigo contagiosa, and in weeping eczemas; internally, in gastro-intestinal catarrh, proctitis, dysentery, bacillary and choleraic diarrhea, cholera infantum.

*Dosage.*—From 1 to 3 Gm. per day to adults; from 0.125 to 0.3 Gm. as a dose to children. Externally (as a dusting powder, in bandages, etc.) like iodoform, in lotions, and in ointments in 3 to 10 per cent strength.

SCHERING & GLATZ, DIVISION OF WM. R. WARNER & CO., INC.

**Xeroform (Powder):** 30 Gm. and 453 Gm. bottles.

U. S. trademark 66,547.

### *Mercury*

Compounds of mercury are used for the preparation of antiseptic and disinfecting solutions. They have a limited germicidal activity for nonsporulating bacteria. They cannot be relied upon to kill bacterial spores even after several hours' exposure. Solutions of compounds of mercury with dyes or other organic radicals have been used for disinfection of the skin, for the treatment of infected wounds and for local treatment of certain bacterial infections. In general these organic compounds of mercury are claimed to be less toxic and less irritating than the older chlorides, iodides and cyanides of mercury. They are highly bacteriostatic and hence may be found to be of distinct value as antiseptics even though their germicidal activity, especially for bacterial spores, has not been conclusively demonstrated. Claims for their ability to penetrate deeply into living tissue and to act as efficient chemotherapeutic agents after injection into the blood stream have not been established. Their antibacterial activity is very greatly diminished in the presence of serum or other proteins.

### *Inorganic*

**MERCURIC CYANIDE-N. F.**— $\text{Hg}(\text{CN})_2$ .—"When dried to constant weight over sulfuric acid, contains not less than 99 per cent of  $\text{Hg}(\text{CN})_2$ ."—N. F.

For description and standards see The National Formulary under Mercuric Cyanide.

*Actions and Uses.*—Mercuric cyanide has been reported to

be as actively antiseptic as mercuric chloride and to be less irritating; but this has been questioned. It is used locally and internally as is mercuric chloride. Blum and Schwab (*Presse Méd.* 30:1081 [Dec. 16] 1922) highly recommended this drug as a diuretic in cardiac (but not in renal) disease. They give it in doses of 40 to 50 mg. by intravenous or intramuscular injection. They state, however, that mercury should be used as a diuretic only as a last resort when other drugs have failed.

*Dosage.*—Internally, from 4 to 8 mg., locally, solutions of from 1 in 4,000 to 1 in 2,000 may be used for applications to the eye or mucous membranes; from 1.5 to 2 cc. of a 1 per cent solution may be used hypodermically without causing local irritation. Death has occurred from the use of a vaginal injection containing 0.9 Gm. of mercuric cyanide.

In diphtheria and croup, it is used in 0.01 per cent solution as a gargle. In fibrinous rhinitis it is used on a tampon in 0.04 per cent solution.

MALLINCKRODT CHEMICAL WORKS

**Mercuric Cyanide (*Powder*):** bulk.

MERCK & Co., INC.

**Mercuric Cyanide (*Powder*):** bulk.

**MERCURIC POTASSIUM IODIDE.**—A complex salt formed by the interaction of one molecule of mercuric iodide with two molecules of potassium iodide and containing about 25.5 per cent of mercury.

For tests and standards, see Section B.

*Actions and Uses.*—Mercuric potassium iodide is used for the same purposes as mercuric iodide, over which it has some advantages because of its solubility. It is germicidal for many nonsporulating bacteria. However, there seems to be no work to show how much the activity is decreased when an excess of potassium iodide is present. In comparison with mercuric chloride it is claimed to have a greater safety factor: Weight for weight, mercuric potassium iodide is about one half as toxic as mercuric chloride according to animal experiments; in proportion to the mercury content, however, mercuric potassium iodide and mercuric chloride possess about the same toxicity.

Externally, mercuric potassium iodide is used for skin disinfection, irrigations and disinfection of instruments and of excreta and discharges.

*Dosage.*—As a disinfectant it is used in concentrations of 1 in 100 to 1 in 10,000. For irrigation of wounds, it is desirable to render the solution isotonic by addition of 0.9 per cent sodium chloride. Solutions of mercuric potassium iodide may be prepared:

- (1) By dissolving 1 part by weight of mercuric iodide and

1 part by weight of potassium iodide in a small amount of water and then diluting to proper strength; such a solution will contain about 20 per cent excess of potassium iodide, sufficient to prevent precipitation of mercuric iodide from dilute solutions of the complex salt. (1 Gm. mercuric iodide is equivalent to 1.7 Gm. mercuric potassium iodide.)

(2) By dissolving mercuric potassium iodide in water containing potassium iodide. Solutions made from mercuric potassium iodide alone have a tendency to decompose with precipitation of mercuric iodide; hence it is necessary to have present an excess of potassium iodide equivalent to about 20 per cent by weight of the amount of mercuric potassium iodide used.

PARKE, DAVIS & COMPANY

**Discs Potassio-Mercuric Iodide:** Each disc represents mercuric iodide 97.2 mg., potassium iodide 97.2 mg. and sodium bicarbonate 2.9 Gm. Colored blue.

**Discs Potassio-Mercuric Iodide:** Each disc represents mercuric iodide 24.3 mg., potassium iodide 24.3 mg. and sodium bicarbonate 1.04 Gm. Colored blue.

**YELLOW MERCURIC OXIDE-U. S. P.**—Yellow Precipitate.—“When dried to constant weight at 110 C., contains not less than 99.5 per cent of  $\text{HgO}$ .”—*U. S. P.*

For description and standards see the *U. S. Pharmacopeia* under Yellow Mercuric Oxide and Yellow Mercuric Oxide Ointment.

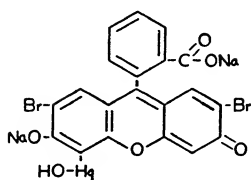
**Actions, Uses and Dosage.**—Yellow mercuric oxide is employed principally as the official ointment which contains a 1 per cent concentration of the salt in wool fat, yellow wax and petrolatum. It is used mainly for application to the eye in the control of superficial infections. Because of its prolonged action frequent applications are unnecessary and undesirable.

MANHATTAN EYE SALVE COMPANY, INC.

**Ointment Yellow Oxide of Mercury 1%, Adrenalin Chloride 2%, and Phenol.**—Yellow oxide of mercury, 1 per cent; solution of adrenalin chloride, 2 per cent; menthol, 0.04 per cent; phenol, 0.2 per cent; anhydrous wool fat, 10 per cent, and white petrolatum sufficient to make 100 per cent. Put up in collapsible tubes, for application to the eye.

### Organic

**MERBROMIN-N.F.**—**Mercurochrome-H. W. & D.**—“The disodium salt of 2,7-dibrom-4-hydroxymercurifluorescein. When dried to constant weight at 110 C. and assayed, Merbromin yields not less than 24 per cent and not more than 26.7 per cent of  $\text{Hg}$  [mercury], and not less than 18 per cent and not more than 21.3 per cent of  $\text{Br}$ . [bromine].”—*N. F.* The structural formula may be represented as follows:



For description and standards see The National Formulary under Merbromin, Merbromin Solution and Merbromin Solution, Surgical.

*Actions and Uses.*—Merbromin is a nonirritating moderately active antiseptic. When applied to the skin, mucous membranes and wounds it exerts bacteriostatic action. The 2 per cent aqueous solution of merbromin acts more slowly than iodine tincture-U.S.P., but has more prolonged bacteriostatic effect. The aqueous-alcohol-acetone solution called merbromin surgical solution is more rapid in its action than the aqueous solution and may be used for preoperative skin disinfection. Merbromin penetrates significantly only into dying or dead tissue.

The drug is tolerated in a strength of 1 per cent by the bladder, renal pelvis and urethra; a 2 per cent solution applied to the anterior urethra causes only temporary discomfort. When tested by intravenous injection into rabbits, the danger point is reached with a dosage of 25 mg. per Kg., and 5 mg. causes a decrease in phenolsulfonphthalein excretion and an albuminuria which lasts about a week. Dogs are more resistant. No systemic effects have been observed following its local application in the human. Merbromin has been used in cystitis and urethritis; also in affections of the eye and affections of the ear, such as otitis media. Although merbromin has been used intravenously the Council does not recognize the use of the drug for this purpose. The intravenous injection may be followed by severe toxic symptoms.

*Dosage.*—In the treatment of infections of the kidney pelvis, the ureters are catheterized and the pelvis gently filled with a 1 per cent solution; the catheter is plugged and the solution retained for five minutes. In the treatment of bladder conditions, 25 to 30 cc. of the 1 per cent solution is introduced into the bladder and retained for one hour or longer, the treatment being given daily or on alternate days, or at longer intervals according to circumstances. Gonococcic infections are treated by more modern drugs. However, when substances such as merbromin are indicated as adjunct treatment, they should be properly used. In anterior gonococcus urethritis, the anterior urethra is filled with a 1 per cent solution and the solution retained for five minutes. If the posterior urethra be involved, the solution is gently retained for an hour or more. In rare cases, considerable irritation is produced, particularly in those with residual urine. Later, in the treatment of acute anterior gonorrhea, a 2 per cent

solution is used every three hours. Solutions should not be boiled. They should be made up from the drug itself, as the tablets are not suitable for this purpose.

Merobromin is incompatible with acids, with the salts of most alkaloids and with most local anesthetics. The aqueous solution stains the skin red but the discoloration may be removed by washing in a solution of sodium hypochloride.

HYNSON, WESTCOTT & DUNNING, INC.

**Mercurochrome (Powder):** bulk.

**Solution Mercurochrome, 2% :**

**Surgical Solution of Mercurochrome:** Merbromin, 2 per cent dissolved in a vehicle consisting of 55 parts of 95 per cent alcohol, 10 parts of acetone, and 35 parts of water, to which has been added sodium carbonate, 0.1 per cent.

**Tablets Mercurochrome:** 0.3 Gm.

U. S. patent 1,535,003 (April 21, 1925; expired). U. S. trademark 197,189.

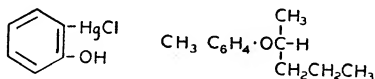
PREMO PHARMACEUTICAL LABORATORIES, INC.

**Merbromin (Crystals):** 10 Gm., 100 Gm., 500 Gm. and 1,000 Gm. bottles.

**Solution of Merbromin:** 7.5 cc., 15 cc., 30 cc., 473 cc. and 3,785 cc. bottles.

**Surgical Solution of Merbromin:** 473 cc. and 3,785 cc. bottles.

**MERCOCRESOLS.**—**Mercresin-Upjohn.**—A mixture consisting of equal parts by weight of secondary amyltr cresol,  $\text{CH}_3(\text{OH})\text{C}_6\text{H}_3\text{CH}(\text{CH}_3)\text{C}_3\text{H}_7$ , and *ortho*-hydroxyphenylmercuric chloride,  $o\text{-HOC}_6\text{H}_4\text{HgCl}$ . Mercocresols is used in the form of a tincture containing secondary amyltr cresol, 0.1 per cent, and *o*-hydroxyphenylmercuric chloride, 0.1 per cent, dissolved in a solution containing 10 per cent acetone, 50 per cent alcohol, and water. The structural formula of mercocresols may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Mercocresols, the combination of cresol derivatives and an organic mercury compound as defined above, possesses germicidal, fungicidal and bacteriostatic properties peculiar to its two component parts. The actions of its two con-



stituents supplement each other so that the mixture is approximately twice as germicidal for *S. aureus* as the component cresol derivatives alone, and seven to ten times as germicidal as the mercury compound alone. The estimated total effect should not be construed to be of that same order for all pathogenic bacteria and should be understood to represent a summation of activity rather than synergistic action of the two components. Its use as a germicide is subject to some of the same shortcomings of ordinary tricresols and organic mercurial antiseptics, particularly with respect to its inability to destroy bacterial spores.

Mercocresols is useful in the form of the tincture described above for external application as an antiseptic for minor superficial wounds or infections and as a prophylactic disinfectant for surgical preparation of the intact skin. Subject to dilutions variously indicated below it is also useful for topical application to mucous membranes and for irrigation of certain body cavities and deep infected wounds.

The toxicity of mercocresols is principally that of the organic mercurial component.

**Dosage.**—Mercocresols is applied topically in the form of the undiluted tincture (containing secondary amyltricresol 1:1000 and *ortho*-hydroxyphenyl mercuric chloride 1:1000) to all superficial wounds and for surgical preparation of the intact skin. It may be similarly applied to the ear, nose and throat, but dilutions of from 1:5 to 1:20 should be used for irrigation or wet packs applied to these surfaces. In general, from 1:2 to 1:20 dilutions are used for topical application, irrigation or tamponage of inflamed mucous membranes depending on the site and the method employed. For irrigation of deep infected wounds or abscesses, dilutions of from 1:5 to 1:10 are recommended; for irrigation, instillation or lavage of the bladder and urethra from 1:10 to 1:20 dilutions should be used. Dilutions of from 1:10 to 1:20 are also employed for instillation in the eye.

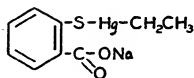
Mercocresols is compatible with both acids and alkalies and does not precipitate with the chlorides of the body fluids.

#### THE UPJOHN COMPANY

**Tincture Mercresin:** 60 cc. (Pistol Grip), 118 cc., 473 cc. and 3.785 liter bottles. A tinted solution of mercocresols, 0.2 per cent in a mixture of acetone 10 per cent, alcohol 50 per cent and water.

**Tincture Mercresin (Stainless):** 118 cc., 473 cc. and 3.785 liter bottles. An untinted solution of mercocresols, 0.2 per cent in a mixture of acetone 10 per cent, alcohol 50 per cent and water.

**MERTHIOLATE-Lilly.**—Merthiolate Sodium.—Sodium ethylmercurithiosalicylate.—Merthiolate contains from 49.15 to 49.65 per cent of mercury in organic combinations. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Merthiolate is bacteriostatic for many non-sporulating bacteria and is also fungistatic. It is used for disinfecting tissue surfaces. However, it should be remarked that this agent, like other organic mercurials presently available, cannot be guaranteed to achieve sterilization, especially when spore-forming organisms are present. Merthiolate is much less toxic than mercuric chloride.

Merthiolate 1:10,000 may be useful as a preservative of biologicals of not too high protein content; this concentration, however, does not necessarily prevent growth of micro-organisms in stored, liquid plasma.

**Dosage.**—For disinfection of instruments, 1 in 1,000 aqueous solution; for application to the intact skin, tincture 1 in 1,000; for application in wounds and to denuded surfaces, aqueous solution 1 in 1,000; for ophthalmologic use, from 1 in 10,000 to 1 in 5,000 aqueous solution; for application to nasal mucous membranes, from 1 in 5,000 to 1 in 2,000 aqueous; for urethral irrigations, 1 in 30,000 to 1 in 5,000 aqueous.

ELI LILLY AND COMPANY

**Jelly Merthiolate 1:1,000:** Merthiolate 0.1 per cent, eucalyptol 0.016 per cent and eugenol 0.016 per cent, in a water soluble base.

**Ointment Merthiolate, 1:1,000:** 28 Gm., 450 Gm. (1 lb.) and 2.26 Kg. (5 lbs.) jars. Merthiolate 0.1 per cent in a hydrophilic ointment base.

**Ophthalmic Ointment Merthiolate 1:5,000:** Contains Merthiolate 1 part in 5,000 parts of a base consisting of wool fat, liquid petrolatum and white petrolatum.

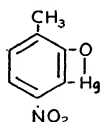
**Solution Merthiolate, 1:1,000:** One gram of Merthiolate and 1 Gm. of monoethanolamine in 1,000 cc. of water, buffered with 1.4 Gm. of sodium borate and containing sodium chloride to make the solution approximately isotonic.

**Suppositories Merthiolate, 1:1,000:** Each suppository weighs approximately 10 Gm. and contains Merthiolate 1:1,000 in a glycerin and gelatin base consisting of 17.3 parts glycerin and 7.6 parts gelatin.

**Tincture Merthiolate, 1:1,000:** Contains Merthiolate, 0.1 Gm., and monoethanolamine, 0.1 Gm., dissolved in alcohol, 50 cc.; acetone, 10 cc., and water, sufficient to make 100 cc.

U. S. Patent 1,672,615 (June 5, 1928; expired); 1,862,896 (June 14, 1932; expires 1949). U. S. trademark 252,182.

**NITROMERSOL-N.F.—Metaphen-Abbott.**—Anhydride of 4-nitro-3-hydroxymercuri-*ortho*-cresol. —  $C_7H_5O_3NHg$ . — “When dried to constant weight at 105 C., Nitromersol yields not less than 56 per cent and not more than 57.4 per cent of Hg.”—*N. F.* When nitromersol is dissolved in alkali, the anhydride ring opens, forming the hydroxymercury salt. The structural formula of nitromersol may be represented as follows:



For description and standards see The National Formulary under Nitromersol, Nitromersol Solution and Nitromersol Tincture.

**Actions and Uses.**—Nitromersol is used only in the form of the sodium salt, which is claimed to be more germicidal than mercuric chloride when tested on cultures of *Staphylococcus aureus* and *Eberthella typhosa*. It is stated to be relatively non-irritating when applied to mucous membranes or the skin and to be without deleterious action on metallic instruments or rubber. Nitromersol is claimed to be relatively nontoxic.

Nitromersol is proposed for use in the treatment of gonorrhea and other infections of the eye; for the disinfection of skin, surgical instruments and rubber if no sporulating pathogenic organisms are present.

**Dosage.**—Solutions of nitromersol in water are prepared with the aid of sodium hydroxide. For disinfection of instruments solutions of 1 in 5,000 to 1 in 1,000; for application to the skin solutions of 1 in 5,000 and 1 in 1,000; for ophthalmologic and for urethral irrigation solutions of 1 in 5,000 to 1 in 10,000 are proposed.

#### ABBOTT LABORATORIES

**Ophthalmic Ointment Metaphen:** Metaphen 1:3,000 in an ointment base containing anhydrous wool fat, 25 per cent, and petrolatum, 75 per cent.

**Solution Metaphen, 1:500:** Metaphen dissolved in water by means of sodium hydroxide to form the sodium salt of nitromersol.

**Solution Metaphen, 1:2,500:** Metaphen dissolved in water containing 0.33 per cent each of sodium bicarbonate and sodium carbonate to form the sodium salt of nitromersol.

**Disinfecting Solution Metaphen for Dental and Surgical Instruments:** 946 cc. and 3,785 cc. bottles. Contains Metaphen 1:2,500 W/V and benzyl alcohol 4.0 per cent in an aqueous solution containing ethylene glycol 20.0 per cent W/V and sufficient

sodium hydroxide and sodium carbonate to neutralize the metaphen.

**Tincture Metaphen, 1:200:** Metaphen, 0.5 Gm., dissolved in a mixture of acetone, 10 cc., water, 40 cc. and alcohol, 50 cc.

U. S. patent reissue 17,563 (Sept. 22, 1925; expired). U. S. trademark 205,507.

### Phenylmercuric Compounds

Phenylmercuric chloride and basic phenylmercuric nitrate were the first of the organic mercurial compounds of their type found to possess effective bacteriostatic and bactericidal activity against certain pathogenic micro-organisms. Evidence to indicate that other phenylmercuric salts are similarly effective suggests that the activity of such compounds is primarily attributable to the phenylmercuric ion, the structural formula of which may be represented as follows:



In general, phenylmercuric salts are highly dissociable in solutions to provide phenylmercuric ions, effective concentrations of which are dependent on the widely varying solubility of the salts employed. In acid, neutral or slightly alkaline solutions, chlorides, bromides, iodides and soaps react with phenylmercuric ion to precipitate a phenylmercuric salt. Phenylmercuric chloride is soluble only to the extent of 1 part in 20,000 of water, the bromide is still less soluble and the iodide is quite insoluble. For this reason the chloride has been supplanted by the more soluble basic phenylmercuric nitrate and other salts.

The phenylmercuric ion ( $C_6H_5Hg$ )<sup>+</sup> is more stable in acid than in alkaline solutions of its salts. Aqueous solutions containing phenylmercuric ions, buffered with inorganic or organic acids, are fairly stable. In the presence of organic solvents the stability is lowered but is still relatively good. Because buffered solutions of phenylmercuric salts are more stable and also less irritating to tissue than unbuffered solutions, they are preferred for pharmaceutical purposes. In general, the buffered solutions are stainless, colorless, odorless, without action on rubber and noncorrosive to the common metals other than aluminum, except as these properties may be influenced by the particular acid employed. Solutions of phenylmercuric salts may develop increasing amounts of mercuric and mercurous ions or free mercury, as the result of gradual decomposition of phenylmercuric ions.

There is evidence to indicate that phenylmercuric compounds are of comparatively high germicidal and inhibitory value

against a variety of pathogenic bacteria and of relatively low toxicity to human tissue. As with the other types of organic mercurial antiseptics, however, they cannot be depended on to kill bacterial spores even after several hours' exposure. The presence of buffered solutions of phenylmercuric salts does not interfere with the precipitin reaction of human serum, the action of complement, the digestive action of pepsin and trypsin or the antigenic power of vaccine. Despite their relatively low toxicity, phenylmercuric compounds may produce irritation, "burns" or poisoning in occasional individuals with undue sensitivity. The minimum lethal intravenous dose for rabbits of a 0.067 per cent (1:1,500) aqueous solution of basic phenylmercuric nitrate (buffered with 0.1 per cent boric acid) is 7 cc. per kilogram of body weight. Other evidence indicates that the minimum lethal oral dose for these animals is approximately three times the intravenous dose. The toxicity of solutions of this and other phenylmercuric salts may be expected to vary according to the concentration of phenylmercuric ions, the presence of organic solvents, the acid which is added as a buffer to render them stable and the degree of decomposition. The appearance of metallic mercury as a precipitate in solutions of phenylmercuric salts indicates extensive decomposition.

#### **PHENYLMERCURIC BORATE TINCTURE 1:500.**

—**Merphenyl Borate Tincture 1:500-Hamilton Labs.**—A tincture consisting of acetone 4.6 per cent, alcohol 43.2 per cent and water 50 per cent, containing phenylmercuric borate 0.2 per cent, with 1.0 per cent each of boric acid and sodium acid phosphate. Phenylmercuric borate can be considered to have the formula  $C_6H_5HgBO_2 \cdot H_2O$ , although a product of this composition may be difficult to isolate. Solutions which can be considered to contain phenylmercuric borate may be prepared by the addition of boric acid in appropriate amounts to solutions of phenylmercuric hydroxide.

For tests and standards, see Section B.

*Actions and Uses.*—Phenylmercuric borate is recognized for use in tincture form for external use as an antiseptic for the prophylactic and therapeutic disinfection of the skin, superficial injuries and wounds. Buffered solutions of this compound are claimed to be somewhat less irritating than certain other phenylmercuric compounds.

*Dosage.*—For prophylactic preoperative preparation of the intact skin, disinfection of recent soft tissue injuries and the treatment of superficial wounds a 1:500 tincture of phenylmercuric borate may be applied full strength; for application to mucous membranes, in wet dressings or continuous irrigation for infected wounds, a 1:24,000 concentration should be used (prepared by diluting the 1:500 tincture approximately forty-five times with water). In wet dressings, undue concentration of the diluted solution from unavoidable evaporation should be prevented by the addition of about 0.5 per cent of sodium

chloride. Approximately  $\frac{1}{2}$  teaspoon of noniodized table salt to each pint of the diluted tincture is recommended. This amount of sodium chloride does not produce excessive precipitation. Dressings and bandages wet with the full strength (1:500) tincture should never be applied.

HAMILTON LABORATORIES, INC.

**Tincture Merphenyl Borate 1:500: bulk.**

U. S. trademark 318,039.

**PHENYLMERCURIC NITRATE-N.F.—Merphenyl Nitrate (Basic)-Hamilton Labs.**—Basic Phenylmercuric Nitrate.— $C_6H_5HgNO_3 \cdot C_6H_5HgOH$ .—"A mixture of phenylmercuric nitrate and phenylmercuric hydroxide containing not less than 62.75 per cent and not more than 63.5 per cent of Hg [mercury]."—*N. F.*

For description and standards see The National Formulary under Phenylmercuric Nitrate.

*Actions and Uses.*—Phenylmercuric nitrate is recognized for external use in solution or ointment as an antiseptic for the prophylactic and therapeutic disinfection of the skin, superficial abrasions, lacerations, wounds and infections.

*Dosage.*—For prophylactic disinfection of the intact skin and minor lesions the 1:1,500 aqueous buffered solutions may be applied full strength; for application to mucous membranes or for the application of wet dressings or continuous irrigation to wounds, a 1:15,000 to 1:24,000 aqueous solution should be used (prepared by diluting the 1:1,500 buffered solution approximately ten to fifteen times with water). When used as a wet dressing, the 1:24,000 dilution should be prevented from becoming too concentrated, as the result of unavoidable evaporation, by the addition of about 0.5 per cent of sodium chloride. Approximately  $\frac{1}{2}$  teaspoon of noniodized table salt to each pint of diluted solution is recommended. This amount of sodium chloride does not produce excessive precipitation. The full strength (1:1,500) solution should never be used to wet bandages or dressings. The 1:1,500 oxycholesterin base ointment may also be employed for the prophylactic disinfection of minor injuries or may be applied twice daily for the treatment of superficial infections.

HAMILTON LABORATORIES, INC.

**Ointment Merphenyl Nitrate (Basic) 1:1,500:** A water-in-oil emulsion ( $\frac{2}{3}$  aqueous,  $\frac{1}{3}$  oil phase) of an oxycholesterin base containing basic phenylmercuric nitrate 0.067 per cent with boric acid 0.1 per cent.

**Solution Merphenyl Nitrate (Basic) 1:1500:** An aqueous solution of basic phenylmercuric nitrate 0.067 per cent with boric acid 0.1 per cent.

U. S. trademark 318,039.

**PHENYLMERCURIC PICRATE TINCTURE 1:200 WITH PICRIC ACID.**—Merphenyl Picrate Tincture 1:200 with Picric Acid—Hamilton Labs.—A tincture consisting of acetone 10 per cent, alcohol 50 per cent and water 38.3 per cent, containing phenylmercuric picrate 0.5 per cent with picric acid (trinitrophenol) 1.2 per cent. Phenylmercuric picrate can be considered to have the formula  $C_6H_5HgOC_6H_2(NO_2)_3$ , although a product of this composition may be difficult to isolate. Solutions which can be considered to contain phenylmercuric picrate may be prepared by the addition of picric acid in appropriate amounts to solutions of phenylmercuric hydroxide.

For tests and standards, see Section B.

*Actions and Uses.*—Phenylmercuric picrate, in an acetone-alcohol tincture with picric acid, is primarily intended as a prophylactic disinfectant in the preoperative preparation of the intact skin and for recent abrasions, lacerations and wounds. It may also be employed in the treatment of superficial infections, particularly when the drying effect of acetone and alcohol is desired. Owing to its staining quality, the picrate compound is useful to delineate the field or area of application. Picric acid is added in sufficient concentration to provide fair stability, but the amount present is also sufficient to exert some disinfectant action in itself. Because of its high toxicity internally, the possibility of poisoning due to absorption of picric acid from applications of the tincture to large denuded areas of the skin or to mucous membranes should be kept in mind.

*Dosage.*—For prophylactic preoperative skin preparation, disinfection of soft tissue injuries and the treatment of superficial infections, tincture of phenylmercuric picrate 1:200 with picric acid 1.2 per cent is applied full strength; in wet dressings or continuous irrigation for infected wounds, a concentration of phenylmercuric picrate not greater than 1:15,000 should be used (prepared by diluting the 1:200 tincture approximately seventy-five times with water). When used as a wet dressing, undue concentration of the diluted solution from unavoidable evaporation should be prevented by the addition of about 0.5 per cent of sodium chloride. Approximately  $\frac{1}{2}$  teaspoon of noniodized table salt to each pint of diluted tincture is recommended. This amount of sodium chloride does not produce excessive precipitation. The full strength (1:200) tincture should never be used to wet dressings or bandages.

HAMILTON LABORATORIES, INC.

**Tincture Merphenyl Picrate 1:200 with Picric Acid:**  
bulk.

U. S. trademark 318,039.

### Silver

Silver compounds are used in medicine to secure caustic, astringent and antiseptic effects. These results are produced by the free silver ions. When caustic effects are desired, silver

nitrate is preferred, because the colloidal compounds of silver are largely or completely lacking in caustic properties. As an astringent, also, silver nitrate is the compound of choice; but it must be used in weaker solutions; silver picrate acts similarly. The antiseptic action of silver nitrate is complicated by irritation, pain, astringency and corrosion. These may be desirable for the destruction of tissue or the stimulation of indolent wounds; but when they are not necessary for such purposes, they may be avoided by the use of colloidal silver preparations.

*Caution: The long continued use of any silver preparation may produce irremediable discoloration of the skin or mucous membrane (argyria).*

### Colloidal Silver Preparations

In these, the silver does not exist to any great extent as free ions; therefore, it does not precipitate chlorides or proteins, and is noncorrosive and relatively or quite nonastringent and non-irritant, but a considerable degree of antiseptic action is retained. This is not proportional to the total silver content, and varies for the different compounds, suggesting that the antiseptic action is due to the liberation of very low concentrations of silver ions, which vary for the different compounds.

The mechanism of the action of colloidal silver preparations is analogous to the late action of silver nitrate. This takes place in two stages: (1) the immediate irritant and germicidal effects produced by the direct application of the free silver ions; and (2) the later, milder antiseptic effects produced by the re-solution of the protein silver compounds that were formed in the first stage. If the second stage alone is desired (i.e., mild antiseptics without irritation), the direct application of the colloid compounds may have advantages over their indirect production from silver nitrate, aside from the avoidance of irritation; for the absence of any coagulation membrane facilitates their access to the cells; they form more concentrated solutions than are likely to be formed from the re-solution of the silver precipitates *in situ*; the colloidal aggregates may be smaller and therefore more reactive; and because of the absence of irritation, they are likely to be more frequently applied and would for that reason secure a more continuous action.

The colloidal silver preparations appear to be quite efficacious for the prophylaxis against gonorrheal infection, evidently killing the organisms on direct contact. Culver (*J. Lab. & Clin. Med.* 3:487 [May] 1918) reports that gonococci in hydrocele broth cultures are killed by momentary exposure to 0.5 per cent mild protein silver or to 0.25 per cent strong protein silver. As regards other organisms, discordant results have been reported.

Metallic silver and insoluble compounds of silver, such as the oxide, the halogen salts (iodide, chloride, etc.) and protein-silver precipitates, may be brought into "colloidal solution"; i.e., if they are sufficiently finely divided, they become miscible



with water, so that they apparently go into solution (such "colloidal solutions" are strictly permanent "suspensions" of the insoluble substance in a state of ultramicroscopic particles). The commercial preparations are for the most part produced by dissolving reduced silver or silver oxide, or some protein-silver precipitate, in an excess of a denatured protein, and drying *in vacuo*. This results in substances that dissolve very freely although somewhat slowly, in water, yielding brown "colloidal solutions" which contain so few free silver ions that they do not readily precipitate chlorides or proteins. They consist of indefinite mixtures of metallic silver, silver oxide, and various silver-protein compounds, all in colloidal form. The proportions of these and the properties of the mixture vary according to the conditions under which they are produced. Although there are many gradations, most of the products on the market fall into a small number of fairly definite therapeutic groups:

- (A) Protein Silver, Strong Type.
- (B) Protein Silver, Mild Type.
- (C) Collargol Type.
- (D) Electric Type.
- (E) Silver Halides.

A. Protein Silver, Strong Type.—Strong protein silver compounds contain the lowest percentage of silver (from 7.5 to 8.5 per cent), but have the strongest germicidal action and are distinctly irritant. They are, therefore, therapeutically intermediate between silver nitrate and mild protein silver. Protargol belongs to this group.

Protargol is said to be prepared by precipitating a "peptone" (albumose) solution with silver nitrate, or with moist silver oxide; dissolving the silver peptonate in an excess of protalbumose; and drying *in vacuo* (Fraenkel).

B. Protein Silver, Mild Type.—Mild protein silver compounds contain from 19 to 25 per cent of silver, but are quite nonirritant. The following products listed in N. N. R. belong to this group: Argyn; Silvol; Solargentum. Argyn is defined as a colloidal compound of silver oxide and serum albumin. Solargentum is prepared from alkali-gelatin, used as a solvent for silver oxide. The solution is then concentrated and dried *in vacuo*.

C. Collargol Type.—This contains a much higher percentage (78) of silver, said to be in the form of metallic silver, reduced to the colloidal form by chemical means, and "stabilized" by "a small percentage of egg albumin with products of oxidation." However, the albumin is denatured, since it does not precipitate on boiling; and it presumably constitutes the greater part of the 22 per cent that is not silver. Collargol, therefore, differs from the preceding class in degree rather than in principle, containing a larger proportion of silver in the form of colloidal-metal and oxide, and a smaller proportion in the form of proteinate.

D. Electric Type.—Metallic silver may be brought into colloidal solution electrically, i. e., by forming an arc between silver

electrodes under water. These solutions are very dilute and are not sufficiently stable for concentration. They are also likely to contain silver oxide, and sometimes ionized silver.

**E. Silver Halides.**—These are mixtures of the colloidal silver salts (ten per cent of silver chloride in Lunosol; 18 to 22 per cent of silver iodide in Neo-Silvol) with suitable diluents. They are not astringent nor irritant, and are used as mild local antiseptics. They have the advantage of being colorless.

**Actions and Uses.**—The colloidal silver compounds are used mainly on mucous membranes, for antiseptics. The strong protein silver group is most effective in this respect, but is slightly irritant and stimulant. The mild protein silver group acts largely as mucilaginous demulcent and protective; and as detergent, by dislodging pus. Collargol acts locally like the protein silver, mild group, but is used mainly to produce systemic reactions.

Eye:	Strong Protein Silver Per Cent	Mild Protein Silver Per Cent
Conjunctivitis, simple purulent or gonorrheal ....	2 to 10	Solution, 25 Ointment, 10
Prophylaxis against ophthalmia neonatorum ....	2 to 10	25
Prophylaxis before ophthalmic operations (several days) .....	.....	25
Corneal ulcers .....	.....	50
Nose and throat.....	0.5 to 10	Spray, 10 to 20 Swab, 25 to 50
Wounds and ulcers.....	.....	1 to 10, solution 10, dusting powder
Gonorrhea:		
Injections—prophylactic...	2	10
Gynecologic practice:		
Solutions .....	2 to 10	25 (tampons of solution in glycerin)
Tampons .....	2	
Ointments .....	5	
Suppositories .....	5	Suppositories, 20 (0.3 Gm.)
Rectal administration:		
Injection .....	2	10
Suppositories .....	5 to 10	20 (0.13 Gm.)
Pyelography .....	.....	2 (solargentum) 50 (cargentos)

The antiseptic efficiency of the silver compounds and their content of silver ions may be compared conveniently by measuring their restraining effect on gas-formation by yeast, according to the method of Dreser, as modified by Pilcher and Sollmann (*J. Lab. & Clin. Med.* 8: 301, 1923). According to this, the following solutions approximately equal the efficiency of a 1 in 1,000 solution of silver nitrate in the same media (*J. Lab. &*

*Clin. Med.* 9:260, 1924): Protargol in water 1 per cent, in physiological solution of sodium chloride 0.125 per cent, in blood 0.9 per cent; and Silvol in water 36 per cent, in isotonic solution of sodium chloride 1 per cent, in blood 3 per cent.

**Dosage.**—The concentrations for mucous membranes range from 0.1 to 10 per cent for strong protein silver; from 5 to 50 per cent for mild protein silver, and from 0.02 to 1 per cent for collargol. These are applied every two to four hours, if possible. Solutions should be recently prepared, and should be protected against light. Ointments and suppositories are used with the same concentrations as the aqueous solutions. Stains on linen are removed by 1 in 1,000 solution of mercuric chloride. The usual concentration for special purposes are shown in the foregoing table.

Since the advent of the sulfonamide compounds and of penicillin the use of silver salts for the treatment of gonorrhea, cystitis, sinusitis and in gynecologic practice has decreased enormously. Moreover the physician using silver salts must constantly keep in mind the possibilities of later argyria. *Because of the danger of absorption and possible production of argyria, solutions of silver salts should not be used for irrigation of the bladder, of the vaginal tract, or of the intestinal tract.*

**(Early Preventive) Treatment of Venereal Diseases.**—The ordinary routine consists in washing the parts thoroughly with soap and water, after which a 2 per cent strong protein silver solution is injected into the urethra and held there for five minutes. The glans is then inuncted with 30 per cent mild mercurous chloride ointment for five minutes.

The efficacy has been marked if the treatment is applied thoroughly within an hour after exposure, and is fair up to three hours. In the A. E. F. of World War I, the ratio of diseases to exposure was about 1 in 30 without prophylactic treatment, and 1 in 90 with treatment. Prophylaxis, therefore, reduced the incidence to about one third (Ashburn, 1919). It is practically useless after five hours.

**COLLOIDAL SILVER CHLORIDE-N. F.**—Lunosol-Hille Labs.—AgCl.—“Silver chloride rendered colloidal by the presence of sucrose or other suitable colloid stabilizing agent. It contains not less than 9 per cent and not more than 11 per cent of AgCl [silver chloride].”—*N. F.*

For description and standards see The National Formulary under Silver Chloride, Colloidal.

**Actions and Uses.**—Aqueous “solutions” of colloidal silver chloride have antiseptic and germicidal properties. Even concentrated solutions cause neither irritation of the mucous membranes nor coagulation of albumin; they do not stain the skin on topical application. Possibilities of argyria from their continued use constantly must be kept in mind.

Solution of colloidal silver chloride are intended for prophylaxis against and treatment of infections of the accessible mucous

membranes, such as the genito-urinary tract and the eye, ear, nose and throat.

**Dosage.**—Colloidal silver chloride is generally used in solutions. In the male urethra, from 3 to 25 per cent; in the genito-urinary tract of the female, 5 to 25 per cent; in inflammatory infections of the eye, ear, nose and throat, 10 to 100 per cent; in ophthalmia neonatorum, 25 to 100 per cent.

#### HILLE LABORATORIES

**Liquid Lunosol:** An aqueous "solution" containing 100 Gm. colloidal silver chloride in each 100 cc. (1 cc. of Liquid Lunosol is equivalent in silver chloride content to 1 Gm.), about 84.5 Gm. sucrose, about 1 Gm. sodium chloride and about 47.8 Gm. water, marketed in 15 cc. and 60 cc. dropper bottles, accompanied by an empty dilution bottle, thus affording a convenient means of preparing the various dilutions which may be indicated; also in 30 cc. and 125 cc. bottles for dispensing.

**Ointment Lunosol 10%:** Liquid Lunosol, 10 cc., incorporated in 90 Gm. of an unguent base composed of about 17 Gm. of water, 55.5 Gm. of anhydrous lanolin and 27 Gm. of liquid petrolatum in each hundred grams.

**COLLOIDAL SILVER IODIDE-N. F.—Neo-Silvol-Parke, Davis.**—AgI.—"Silver iodide rendered colloiddally stable by the presence of gelatine. It contains not less than 18 per cent and not more than 22 per cent of AgI [silver iodide]."

For description and standards see The National Formulary under Silver Iodide, Colloidal.

**Actions and Uses.**—Colloidal silver iodide, even in concentrated "solutions," causes neither irritation of mucous membranes nor coagulation of albumin. It does not stain the skin on topical application. Possibilities of argyria from its continued use must constantly be kept in mind.

Colloidal silver iodide is intended for prophylaxis against, and treatment of, infections of accessible mucous membranes, especially of the genito-urinary tract and of the eye, ear, nose and throat.

**Dosage.**—In the treatment of acute inflammations of the mucous membranes solutions of colloidal silver iodide as strong as 50 per cent may be used. In inflammatory infections of the ear, nose and throat, 5 to 40 per cent solutions are used; for irrigating sinuses 2 to 5 per cent; for inflammatory conditions of the eye and conjunctival infections a strength of 10 to 40 per cent; as urographic medium, 20 per cent.

Solutions of colloidal silver iodide are prepared by adding the substance to the required amount of water (hot, for concentrations of 25 per cent or over) and agitating the mixture until solution occurs.

Solutions tend to precipitate gradually after standing longer

than a week. Local anesthetics should not be added to solutions of colloidal silver iodide.

*"Caution: Solutions of Colloidal Silver Iodide should be freshly prepared and should be dispensed in amber-colored bottles."*—N. F.

PARKE, DAVIS & COMPANY

**Neo-Silvol (Granules):** bulk.

**Capsules Neo-Silvol:** 0.39 Gm.

**Ointment Neo-Silvol 5%:** Neo-silvol, 5 per cent, in a base composed of glycerin, benzoinated lard, hydrous wool fat and petrolatum.

**Vaginal Suppositories Neo-Silvol:** Neo-silvol, 0.454 Gm. in a base composed of gelatin, glycerin and water.

U. S. patent 1,610,391 (Dec. 14, 1926; expired). U. S. trademark 157,369.

**MILD SILVER PROTEIN-U. S. P.—Argyn-Abbott.—Silvol-Parke, Davis.—Mild Silver Protein.—Mild Protargin.—**  
"Silver rendered colloidal by the presence of, or combination with, protein. It contains not less than 19 per cent and not more than 23 per cent of silver (Ag)."

For description and standards see the U. S. Pharmacopeia under Silver Protein Mild.

*Actions, Uses and Dosage.*—See general article, Colloidal Silver Preparations. Possibilities of argyria from its continued use must constantly be kept in mind.

*"Caution.—Solutions of Mild Protein Silver should be freshly prepared and should be dispensed in amber-colored bottles."*  
U. S. P.

ABBOTT LABORATORIES

**Argyn (Powder):** 30 Gm., 120 Gm. and 453 Gm. bottles. A colloidal compound of silver oxide and serum albumin.

**Tablets Argyn:** 0.39 Gm.

U. S. trademark 137,522.

PARKE, DAVIS & COMPANY

**Silvol (Powder):** bulk. A colloidal compound of silver with an alkaline protein.

**Capsules Silvol:** 0.39 Gm.

**Vaginal Suppositories Silvol, 5%:** Suppositories weighing 8.45 Gm. and containing silvol, 5 per cent, in a base composed of gelatin and glycerin.

**STRONG PROTEIN SILVER-N. F.—Protargol-Winthrop.—Strong Silver Protein.—Strong Protargin.**—"Contains not less than 7.5 per cent and not more than 8.5 per cent of Ag [silver]."—N. F.

For description and standards see The National Formulary under Strong Protein Silver.

*Actions, Uses and Dosage.*—See the general article, Colloidal Silver Preparations. Solutions are best prepared by dusting the powder on the surface of cold water, and allowing it to dissolve without stirring or shaking. This requires about ten minutes. Solutions should be freshly prepared. Possibilities of argyria from its continued use must constantly be kept in mind.

*“Caution.—Solutions of Strong Protein Silver should be freshly prepared and should be dispensed in amber-colored bottles.” N. F.*

MERCK & Co., INC.

**Silver Protein Strong (Powder):** bulk.

WINTHROP-STEARNs, INC.

**Protargol (Powder):** 30 Gm. bottle. A colloidal compound of silver-albumose.

**Protargol Compound (Granules):** 30 Gm. bottle. Protargol, 33⅓ per cent, and urea, 66⅔ per cent, added to increase the solubility.

U. S. trademark 30,882.

### Silver Salts

**SILVER NITRATE-U. S. P.**—“When powdered and dried to constant weight in the dark over sulfuric acid for 4 hours, contains not less than 99.8 per cent of  $\text{AgNO}_3$ .” U. S. P.

For description and standards see the U. S. Pharmacopeia under Silver Nitrate.

ABBOTT LABORATORIES

**Solution Silver Nitrate 1%:** 0.5 cc. wax ampul.

ARZOL CHEMICAL COMPANY

**Applicators Silver Nitrate:** Silver nitrate, 75 per cent, and potassium nitrate, 25 per cent, fused to one end of 3 inch and 6 inch wooden sticks. Each applicator is to be used but once.

PARKE, DAVIS & COMPANY

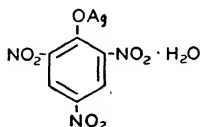
**Capsules Solution Silver Nitrate, 1%:** 0.4 cc. paraffin lined beeswax capsules.

U. S. patent 1,527,659 (Feb. 24, 1925; expired).

SHARP & DOHME, INC.

**Solution Silver Nitrate, 1%:** 0.2 cc. beeswax ampul.

**SILVER PICRATE.**—Picragol-Wyeth.—Silver trinitrophenolate monohydrate. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Silver picrate has actions and uses similar to those of the other simple silver salts. Its crystals are available for making solutions of appropriate strength for use in the treatment of urethritis and infection of Bartholin's and Skene's glands by *Trichomonas vaginalis*, and *Monilia albicans* vaginitis. The aqueous solution or jelly is used in the treatment of gonococcal acute anterior urethritis and the suppositories may be used in the treatment of gonorrheal vaginitis in children. It is also used in the form of a compound powder in the treatment of vaginitis due to *Trichomonas vaginalis* and *Monilia albicans*. This compound powder contains 1 per cent silver picrate in purified kaolin. It is administered by means of an insufflator or other surgical "powder blower." Another dosage form is intended primarily to be used as an adjunct in the treatment of this condition—vaginal suppositories containing 0.13 Gm. in a boroglyceride gelatin base. Protracted use of this compound over a long period may possibly give rise to argyria because of its silver content and nephritis because of its picric acid content. It is therefore necessary to watch the skin for signs of argyria, and the urine for albumin and casts. Possibilities of argyria from its continued use must constantly be kept in mind. In all vaginal insufflation in the pregnant female, the physician should exercise every precaution to prevent positive pressure in the vagina because of danger of breaking the enlarged veins and introducing air into the venous circulation.

**Dosage.**—Dilutions of from 1 to 2 per cent are used in the form of solution compound powder and vaginal suppositories.

WYETH, INCORPORATED

**Picragol (Crystals):** 2 Gm. bottle.

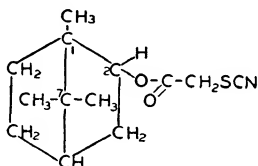
**Picragol Compound 1% (Powder):** Silver picrate, 1 per cent, in purified kaolin.

**Vaginal Suppositories Picrayol:** 0.13 Gm. Silver picrate in a boroglyceride gelatin base.

U. S. trademark 421,338.

## Pediculicides

**ISOBORNYL THIOCYANOACETATE - TECHNICAL.**—The technical grade of isobornyl thiocyanacetate contains 82 per cent or more of isobornyl thiocyanacetate with other terpenes. The structural formula of isobornyl thiocyanacetate may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Isobornyl thiocyanacetate is one of the thiocyanates shown to be effective as a pediculicide. A mixture of the technical grade of this compound with dioctyl sodium sulfosuccinate in the form of an oil emulsion is useful for external application to eradicate both the adult and ova forms of *Phthirus pubis*, *Pediculus humanus capitis* and *Pediculus humanus corporis*. Skin irritation studies reveals that the compound may act as a mild primary irritant to the skin of some individuals, but there is no evidence that it acts as a sensitizing agent. *It should not be applied too near the eyes or to mucous membranes.*

**Dosage.**—An oil emulsion containing isobornyl thiocyanacetate—technical 5 per cent and dioctyl sodium sulfosuccinate 0.6 per cent is applied externally in amounts of 30 to 60 cc. depending on the site involved (quantity of hair), worked into a lather, and allowed to remain for from five to ten minutes. In the case of the scalp, the hair is then combed, permitted to dry and the emulsion left on over night. The head is washed the following day. In the case of the pubis and other regions of the body, the emulsion is worked into a lather and then washed off with soap and water. Care must be taken that the emulsion does not remain in contact with the skin for too long a time. More than two such applications should be avoided.

WYETH INCORPORATED

**Lotion Bornate:** 60 cc. and 3.785 liter bottles. An emulsion containing isobornyl thiocyanacetate 5 per cent, dioctyl sodium sulfosuccinate 0.6 per cent in mineral oil 5 per cent gelatin 0.6 per cent and water.

## Peroxides

Hydrogen peroxide is a combination of two atoms of hydrogen with two atoms of oxygen, one of the latter being given off to oxidizable substances, leaving a residue of water. In the



presence of catalase, a ferment found in all cells, it is readily decomposed. The liberated oxygen sometimes causes considerable effervescence. For this reason it is dangerous to inject it into closed body cavities or into abscesses from which the gas has not a free exit. Hydrogen peroxide solution is official in the U. S. Pharmacopeia. This preparation is germicidal when diluted with not more than twice its volume of water. Diluted with an equal volume of water it destroys typhoid bacilli in two and one-half minutes.

Metallic peroxides are compounds in which the hydrogen of hydrogen peroxide has been replaced by metals, and which are readily decomposed with liberation of hydrogen peroxide, or of oxygen.

*Actions and Uses.*—Like hydrogen peroxide, the metallic peroxides depend for their value on the readiness with which a part of their oxygen becomes active. They are claimed to possess advantages over solution of hydrogen peroxide, because the oxygen is set free more gradually. Among themselves the metallic peroxides differ in their action in accordance with their solubility and the alkalinity produced by interaction of the peroxide with water. The action of peroxides is also affected by the nature of the metal which goes into solution when the peroxide is decomposed. Thus, the use of sodium peroxide is limited by the strong base formed when it dissolves in water.

Aqueous suspensions of zinc peroxide have been found useful in the local treatment of certain wound infections such as those caused by microaerophilic or anaerobic organisms; infections caused by some aerobes, including hemolytic streptococci, have also responded to such treatment.

Because of the strong oxidizing effects on the lower organisms, the peroxides have been recommended as a convenient means of sterilizing water.

**SODIUM PEROXIDE.**— $\text{Na}_2\text{O}_2$ .—The sodium compound analogous to hydrogen peroxide, containing at least 90 per cent of sodium peroxide.

For tests and standards, see Section B.

*Actions and Uses.*—Sodium peroxide is not used internally, but has been used in acne, applied in the form of a paste prepared with liquid paraffin, or as a soap to remove comedones.

MERCK & Co., INC.

**Sodium Peroxide (Powder):** bulk. Contains not less than 96 per cent of sodium peroxide.

**ZINC PEROXIDE MEDICINAL-U. S. P.**—"Consists of a mixture of zinc peroxides, zinc oxide and zinc hydroxide. It contains not less than 45 per cent of  $\text{ZnO}_2$ ."—U. S. P.

For description and standards see The U. S. Pharmacopeia under Zinc Peroxide, Medicinal.

*Actions and Uses.*—See general article, Peroxides.

*Dosage.*—Zinc peroxide medicinal (powder) sterilized in small quantities (10 to 50 Gm.) by heating in a dry oven for four hours at *exactly* 140 C. is made up with sterile distilled water to a smooth, creamy suspension of about the consistency of heavy (40 per cent) cream. The dose depends entirely on the size of the wound to be treated. Enough of the creamy suspension should be used to provide the surface of the wound with a layer approximately  $\frac{1}{8}$  inch thick. If the suspension is too thin it runs off. If it is too thick it may not come in contact with all surfaces in the crevices of the wound. The suspension should be a cream and not a paste. The first layer, applied readily with a syringe, is then covered over with a thin layer of cotton soaked in the suspension and this in turn covered with a thick layer of cotton wet with water and then sealed with an impermeable covering or coating of some kind. Dressings are usually changed in twenty-four hours but may be left for several days.

MALLINCKRODT CHEMICAL WORKS

**Zinc Peroxide 45% -  $\text{ZnO}_2$  Medicinal (Powder):** 30 Gm., 113 Gm. and 453 Gm. bottles.

MERCK & Co., INC.

**Zinc Peroxide-Special Medicinal (Powder):** 15 Gm., 30 Gm., 113 Gm. and 453 Gm. bottles.

### Scabicides

**BENZYL BENZOATE, U. S. P.**— $\text{C}_{14}\text{H}_{12}\text{O}_2$ .—A clear, colorless oily liquid with slight aromatic odor employed externally in various emulsions containing 25 to 30 per cent.

For standards, see U. S. Pharmacopeia under Benzyl Benzoate and Benzyl Benzoate Lotion.

*Actions and Uses.*—Benzyl benzoate applied externally in the form of a 25 to 30 per cent emulsion or lotion has been found to be an effective scabicide. Although, reported to be somewhat effective also as a pediculicide, its use for pediculosis uncomplicated by scabies is not recommended. Application is occasionally followed by a slight, transitory burning sensation. Rarely, severe skin irritation may occur in patients with particularly sensitive skins. It should never be allowed to come in contact with the eyes.

*Dosage.*—A 25 to 30 per cent lotion or emulsion of benzyl benzoate is applied with a swab or brush over the entire body surface (*except the face*) while the skin is still damp immediately following scrubbing of the lesions in a 10-minute soap-warm water bath. Care should be taken to insure application to and around the nails. The first application is allowed to dry and a second application made to the most involved areas. Children ordinarily require 60 cc. to 90 cc. and adults 120 cc. to 180 cc. for a single treatment. Adequate sterilization of bed and body clothing is essential. Twenty-four hours later, clean clothing is

put on after a warm soaking bath. A second or third treatment following the same routine should be carried out if necessary to eradicate the parasite. Secondary pyogenic infections do not contraindicate treatment, but should receive appropriate measures.

GEORGE A. BREON AND COMPANY

**Lotion Benylate:** 120 cc., 480 cc. and 3,840 cc. bottles. An oil in water emulsion containing 25 per cent of benzyl benzoate and approximately 2 per cent of triethanolamine stearate. The product is required to be labeled as Modified Benzyl Benzoate Lotion because it differs from the official benzyl benzoate lotion, U. S. P. essentially by the emulsifying agent used in its preparation.

**PYRETHRUM OINTMENT.**—An ointment containin an extract from powdered pyrethrum flowers (*Chrysanthemum cinerariaefolium*). The extract is obtained by treating powdered pyrethrum flowers with a hydrocarbon oil of the kerosene type; this extract is then incorporated into an ointment base composed of hydrous wool fat, petrolatum and paraffin. The finished ointment contains 27 per cent of the active extract (representing 0.75 per cent of pyrethrins I and II) and 73 per cent of ointment base.

For tests and standards, see Section B.

*Actions and Uses.*—Pyrethrum ointment-Upsher Smith has been shown to be an effective agent in the treatment of scabies. Based on the investigations of Sweitzer and Tedder (*Minnesota Medicine* 18:793, 1935), and Sweitzer (*Journal Lancet* 56:467, 1936), the claim is made that the ointment penetrates the burrows and kills both the mites and the eggs and that except in rare instances it does not produce dermatitis with resultant exfoliation. Sweitzer and Tedder reported four cases of allergic sensitivity to the active substance in a series of 618 patients treated, while Sweitzer found only one case of sensitivity (after three months' use) in 595 additional cases.

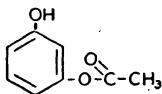
*Dosage.*—The ointment is applied to the entire body following a thorough cleansing with soap and water. Further applications are made on at least three or four successive days. In most cases it is necessary to continue the treatment for a period of from five to seven days, and in obstinate cases the use of the ointment may be required for a longer time. The ointment should not be used on patients who are sensitive to pyrethrum flowers.

UPSHER SMITH COMPANY

**Ointment Pyrethrum:** 100 Gm. and 2.7 Kg. containers.

## Resorcin Compounds

**RESORCINOL MONOACETATE - N.F. — Euresol-Bilhuber-Knoll.**—*m*-Hydroxyphenyl Acetate.—The structural formula may be represented as follows:



For description and standards see The National Formulary under Resorcinol Monoacetate.

*Actions and Uses.*—The action of resorcinol monoacetate is similar to that of resorcinol, but milder and more lasting because of the gradual liberation of resorcinol. Moreover, resorcinol monoacetate in contrast to resorcin does not give a greenish tint to light or gray hair.

Resorcinol monoacetate is used as an adjuvant in the treatment of acne, of sycosis vulgaris, of alopecia and of seborrhea.

*Dosage.*—Resorcinol monoacetate is applied in ointments of from 5 to 20 per cent and in acetone solution. For scalp lotions, alcohol solutions of from 3 to 5 per cent of resorcinol monoacetate are used.

BILHUBER-KNOLL CORP.

**Euresol pro Capillis (Powder):** Resorcinol monoacetate with isopropyl alcohol 6 per cent, perfumed to render it suitable for scalp lotions, supplied in 30 Gm. and 240 Gm. bottles.

U. S. trademark 88,894.

EASTMAN KODAK COMPANY

**Resorcinol Monoacetate (Liquid):** bulk.

## Sulfoichthyolate Preparations and Substitutes

Preparations containing as their essential constituents salts or compounds of a mixture of acids containing sulfur and designated by the group name "sulfoichthyolic acid" are obtained from certain bituminous shales. Sulfoichthyolic acid is characterized by a high sulfur content, the sulfur existing largely in the form of sulfonates, sulfones and sulfides. The ammonium compound of this so-called sulfoichthyolic acid—first introduced as ichthyol—has been used most extensively. Compounds with sodium and other metals, with albumin, with formaldehyde, etc., have also been introduced.

A number of more or less related compounds of sulfur have been introduced as substitutes for the sulfoichthyolates; and the National Formulary contains a sulfoichthyolate preparation under the title, "Ichthammol."

*Actions and Uses.*—The current estimate of the effects of sulfoichthyolic acid preparations is based largely on the use of ichthyol. The use of sulfoichthyolate preparations is still largely empiric. They are weakly antiseptic and emollient. Taken internally, they produce some gastro-intestinal irritation, with diarrhea, etc.

They were formerly used locally under the supposition that they secure the absorption of swellings and effusions in contusions, burns, etc., and especially in gynecologic practice, and in various skin diseases. They have been tried internally in a great variety of conditions, but there is no evidence that they are of any therapeutic value when used in this way.

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## CHAPTER V

# Systemic Anti-Infectives

Systemic anti-infectives are broadly classified to include therapeutic agents administered internally, either orally or parenterally, against infection in its broadest sense. Thus the chapter includes antibacterial, antibiotic, antimalarial antiprotozoan, antirickettsial and anthelmintic drugs as well as those effective in certain virus and fungus diseases. Some of the anthelmintics and the so-called urinary or intestinal antiseptics, though used principally for their local effect, are included because they are administered internally. Others that may be used, both locally and internally, are included in this or the chapter on Local Anti-Infectives on the basis of the principal method of application, as nearly as this can be determined.

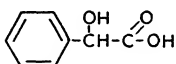
The inhibitory effect of *para*-aminobenzoic acid upon sulfonamide activity is frequently effectively utilized in blood or other cultures to isolate bacterial infection in patients already under treatment with a sulfonamide compound. It should therefore be borne in mind that agents possessing a *para*-aminobenzoyl group as part of their chemical structure, notably procaine and related local anesthetics, are capable of inhibiting the activity of sulfonamides, especially when the latter are administered to control infection in a specific region that is the site of local anesthesia for surgical intervention.

### Antibacterial Agents

#### Chaulmoogra Derivatives

Chaulmoogra Oil and ethyl chaulmoograte are described in The National Formulary. Chaulmoogra oil has been used in the treatment of leprosy for many years. The evidence behind this use indicated that it might be of possible value, though not having specific curative properties. However, experienced observers consider the oil and its derivatives valueless in the treatment of leprosy. Further, cases for treatment with this drug and its derivatives must be selected with great care or much harm may be done. The Council on Pharmacy and Chemistry has given consideration to the status of these agents and is of the opinion that the evidence now available does not support claims for the use of chaulmoogra oil and its derivatives for the treatment of leprosy. However, ethyl chaulmoograte is reported to have been found to be of definite value in sarcoidosis (Schaumann's Disease) formerly spoken of as Boecks Sarcoid.

**MANDELIC ACID-N. F.**—Racemic Mandelic Acid.—“When dried over sulfuric acid for 18 hours, contains not less than 99 per cent of  $\text{HC}_8\text{H}_7\text{O}_3$ .” *N. F.* Mandelic acid has the following structural formula:



For description and standards see The National Formulary under Mandelic Acid.

**Actions and Uses.**—Mandelic acid is a nonmetabolizable substance which when administered by mouth is excreted unchanged in the urine, and if the *pH* of the urine is kept at 5.5 or less it is rendered bactericidal or bacteriostatic against *Escherichia coli*, *Aerobacter aerogenes*, *Streptococcus faecalis* and organisms of the *Proteus*, *Pseudomonas*, *Alcaligenes*, *Salmonella* and *Shigella* groups. The acidity should be controlled by frequent determinations of the *pH*. In cases in which the acidity is not reduced to *pH* 5.5 or less, other acidifying agents such as ammonium chloride, ammonium nitrate or nitrohydrochloric acid may be administered concurrently providing there are no contra-indications. For the same purpose the ketogenic diet has also been employed. Fluid intake should be restricted to an amount not exceeding 1,200 cc. daily. It is usually neither necessary nor advisable to continue mandelic acid therapy longer than from twelve to fourteen days, as renal irritation may ensue. Nausea, diarrhea, dysuria and hematuria may also occur occasionally, requiring reduction in dosage or interruption of therapy. Mandelic acid should not be administered in the presence of renal insufficiency, as an inadequate concentration is obtained in the urine; renal irritation may result, and serious acidosis may occur from retention of the acid.

**Dosage.**—The usual dosage is 3 Gm. four times a day either as the free acid or in the form of the sodium or ammonium salt. An additional acidifying agent is usually required when the sodium salt is employed.

GANE AND INGRAM, INC.

**Mandelic Acid (Powder):** bulk.

MALLINCKRODT CHEMICAL WORKS

**Mandelic Acid (Powder):** bulk.

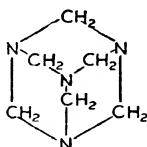
MERCK & Co., INC.

**Mandelic Acid (Powder):** bulk.

### *Methenamine Compounds*

**METHENAMINE-U. S. P.**—Formin-Merck.—Urotropin-Schering & Glatz, Division of Wm. R. Warner & Co., Inc.—Hexamethylenamine.—Hexamethylenetetramine.—“When dried over sulfuric acid for 4 hours, contains not less

than 99 per cent of  $C_6H_{12}N_4$ ." U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Methenamine and Methenamine Tablets.

**Actions and Uses.**—Methenamine owes its action entirely to the liberation of formaldehyde, which occurs only in acid fluids. It is an active urinary antiseptic, provided the urine is secreted in an acid state. It has been shown that no antiseptic effects can occur in the body tissue and fluids which have a neutral or slightly alkaline reaction. Methenamine is not a uric acid solvent, and it has not given satisfactory results in gout. As a urinary antiseptic it is used less extensively, because there are other more effective agents.

Methenamine compounds simply possess the actions of methenamine and of the salts of the acid with which it may be combined.

Methenamine may produce urticaria on local application and, exceptionally, after internal administration. The liberation of formaldehyde in the bladder may cause vesical irritation.

**Dosage.**—0.3 to 0.5 Gm. in half a glass of water every four hours. If the urine is not acid, sodium biphosphate should be administered every four hours in doses of 1 to 2 Gm. midway between the doses of methenamine. Enough sodium biphosphate should be used to render the urine acid, but not enough to cause diarrhea.

#### ABBOTT LABORATORIES

**Tablets Methenamine:** 0.3 Gm. and 0.5 Gm.

#### MERCK & Co., INC.

**Formin (Crystals):** bulk.

U. S. trademark 152,230.

#### THE WM. S. MERRELL COMPANY

**Tablets Methenamine:** 0.325 Gm. and 0.5 Gm.

#### E. S. MILLER LABORATORIES, INC.

**Tablets Methenamine:** 0.3 Gm.

#### SCHERING & GLATZ, DIVISION OF WM. R. WARNER & Co., INC.

**Urotropin (Crystals):** 30 Gm. and 453 Gm. bottles.

**Tablets Urotropin:** 0.3 Gm. and 0.5 Gm.

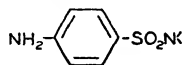
U. S. trademark 269,754.



### Sulfonamide Compounds

The group of compounds referred to as sulfonamides contain in common the chemical group  $-\text{SO}_2\text{N}<$ . The therapeutically active members of this group which have been accepted by the Council are derivatives of the sulfonamide called sulfanilamide

and are characterized by the group—



which may, in addition, carry a single substituent on the *para*-amino group.

Sulfonamide compounds produce many and varied toxic reactions. Hence patients who are being treated with these drugs should be seen at frequent intervals by their physicians in order that the early symptoms and signs of toxicity may be noted and the drug stopped.

*Actions and Uses.*—The exact mode of action of the sulfonamide compounds on susceptible bacteria is still uncertain. Experimental evidence indicates that these compounds may interfere with the proper functioning of certain enzyme systems essential to the multiplication or survival of bacteria. Thus, if a sulfonamide drug is present in the tissues in relatively low concentrations (as is generally true when these drugs are administered by the oral route), the rate of multiplication of susceptible bacteria is decreased (bacteriostatic effect), while if the drug is present in high concentrations (as occurs in the urine) an actual killing (bactericidal) effect may be noted on susceptible microorganisms.

In addition to this primary or direct effect of sulfonamide compounds on certain bacteria, a secondary factor, namely the host effect, may play a part in ridding the infected individual of invading bacteria. This has been especially studied in the instance of hemolytic streptococcic and pneumococcic infections, in which it has been demonstrated that the phagocytosis of these organisms noted in the course of sulfonamide therapy of these infections constitutes an important mechanism in bringing about the complete elimination of the infection. To what extent phagocytosis is important in other infections which are known to be susceptible to sulfonamide therapy has not as yet been established.

It has been demonstrated in the test tube that the addition of substances to culture mediums which act as growth factors for bacteria may decrease the bacteriostatic or bactericidal effects of the sulfonamides. *Para*-aminobenzoic acid, a simple organic chemical which has been isolated from yeast and which is widely distributed throughout nature, possesses marked antisulfonamide effects and is capable of neutralizing relatively large amounts of the various sulfonamide compounds. This observation is of especial importance when one considers that many local anesthetics (procaine is a good example) are esters of *para*-aminobenzoic acid and hence break down in part to the parent

substance when injected into the tissues. Pus and necrotic tissue have also been demonstrated to possess antisulfonamide properties.

The choice of the sulfonamide compound which is to be used in the control of known infections should not be based on caprice or chance but on bacteriologic diagnosis, experience dictated by knowledge of the experimental therapeutic background of these drugs, their pharmacologic properties in man, their clinical efficacy and finally, the variety, frequency and severity of the toxic reactions which may be produced by the drug.

When all these factors are taken into consideration, the following recommendations may be made at the present time concerning the selection of the proper drug for treating a given systemic infection: In hemolytic streptococcus infections due to Lancefield's Group A organisms, sulfadiazine, sulfamerazine and sulfapyrazine are the drugs of choice, with sulfanilamide second, and sulfathiazole third. Pneumococcal infections are best treated with sulfadiazine or sulfamerazine. Sulfathiazole is the second drug of choice in these infections. On the basis of existing evidence sulfathiazole or sulfadiazine are the drugs of choice in the treatment of gonococcal infections. Sulfadiazine, sulfamerazine or sulfathiazole is the drug of choice in the treatment of staphylococcal infections. Meningococcal infections respond well to therapy with sulfadiazine, sulfamerazine, sulfapyrazine, sulfathiazole or sulfanilamide, but current evidence indicates that sulfadiazine and sulfamerazine are the drugs of choice. Sulfadiazine is indicated for use in Friedländer's bacillus infections, with sulfathiazole second. *Shigella dysenteriae* and *H. influenzae* infections are among those most likely to respond to sulfadiazine therapy. Recently a number of authors have proposed the oral administration of sulfadiazine for the treatment of gonococcal ophthalmia. It is believed that such use of sulfonamides shortens the period of active infection and diminishes the likelihood of ophthalmic complications.

The clinical evidence as to the effectiveness of sulfonamide compounds in the control of alpha-hemolytic streptococcus infections, is not completely clear. In tissue infections (other than subacute bacterial endocarditis) produced by the so-called "mouth varieties" of the organism, sulfadiazine or sulfathiazole seem to be about equally effective. None of the sulfonamides are active against the enterococcus group of streptococci. Sulfathiazole is the drug of choice in the treatment of chancroid. Acute bacillary dysentery responds well to sulfadiazine, sulfathiazole, succinylsulfathiazole, sulfaphthalidine and sulfaguanidine. Sulfadiazine is the drug of choice. Sulfadiazine should, on the basis of current evidence, be used in the therapy of actinomycosis. In general, urinary tract infections respond best to the sulfonamide drugs which are recommended for use in tissue infections produced by the same organism. *Anaerobic streptococcus infections, regardless of their location, do not respond to sulfonamide therapy.*

While reports of the definite clinical efficacy of the sulfonamide compounds are extant in respect to hemolytic streptococci Groups B and C, *Brucella melitensis*, *Pasteurella tularensis*, *Clostridium perfringens*, *Clostridium septicum*, *Hemophilus influenzae* and certain other bacterial infections, definite experimental and clinical data which would justify the selection of drugs of choice in infections caused by these organisms are not available at the present time, and the treatment of disease produced by these organisms with the sulfonamides must be regarded still as being problems of clinical investigation.

Four diseases of probable viral origin—trachoma, follicular conjunctivitis, lymphogranuloma venereum and molluscum contagiosum—respond to sulfonamide therapy. Clearcut data which permit one to judge the relative clinical efficiency of the various sulfonamide compounds in these infections are not available. The bulk of the clinical reports on these diseases deal with the therapeutic use of sulfanilamide, sulfathiazole or sulfadiazine. Further, while some cases of molluscum contagiosum no doubt respond to sulfonamide therapy, other less potent medicaments which may be applied locally offer equal therapeutic results.

Sulfadiazine has been demonstrated as an effective agent against the carriers of the meningococcus organism. Two grams a day for two days is usually adequate for treating carriers.

Sulfapyradine is now known to have limited usefulness and would seem to be principally of value in the treatment of dermatitis herpetiformis. The toxic properties of this drug make it unsatisfactory for general systemic use.

There are numerous communications attesting the efficacy or lack of value of the sulfonamides in diseases in which the etiology is ill defined, such as pemphigus vulgaris, dermatitis herpetiformis and lupus erythematosus disseminatus. At the present time the effect of the sulfonamide drugs in these diseases cannot be evaluated. *It appears quite certain that these compounds are ineffective in rheumatoid arthritis and are dangerous in the acute or active phase of rheumatic fever.*

At the present time the Council feels that the evidence for the peroral prophylactic use of sulfonamides in rheumatic fever and for the prevention of pneumonia and other complications of common colds, influenza or measles is unclear, and their use should not be generally recommended.

Laboratory studies have shown that the sulfonamides may be bound to plasma protein, the percentage of binding varying with the drugs, apparently being lowest for sulfanilamide (about 20 per cent) and highest with sulfamerazine (about 80 to 85 per cent); sulfapyrazine and sulfathiazole may show binding as high as 50 and 75 per cent respectively. These studies have raised a question whether such binding makes the sulfonamide ineffective as an anti-infective agent. The available evidence indicates that the protein does not truly inactivate the sulfonamide. It should be remembered that even when the sulfonamides are bound to proteins in the blood, they are gradually released with the passage of time. Thus even though one of two com-

pared sulfonamide compounds may have a greater tendency to bind with the plasma protein, any differences in therapeutic effects cannot be attributed solely to such protein binding.

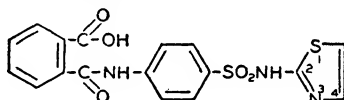
Experience gained in World War II seems to indicate that the use of crystalline sulfonamides and of sulfonamide ointments, creams, lotions, etc. as topical agents was not very successful in the management of wound infection or in treatment of infections of the skin or mucous membrane. The routine use of sulfonamides as topical applications in wounds, burns and in superficial infections is therefore to be discouraged.

*Determination of the Sulfonamides in Body Fluids.*—It is always desirable to determine the values for the sulfonamides in the blood and body fluids at frequent intervals by the method described by Bratton and Marshall (*J. Biol. Chem.* 128: 537, [May] 1939).

Since the dosages suggested below are based on body weight in the metric system, the following table of approximations may be convenient for translating pounds into kilograms:

11 pounds = 5 kilograms	110 pounds = 50 kilograms
22 pounds = 10 kilograms	132 pounds = 60 kilograms
33 pounds = 15 kilograms	154 pounds = 70 kilograms
44 pounds = 20 kilograms	176 pounds = 80 kilograms
55 pounds = 25 kilograms	198 pounds = 90 kilograms
66 pounds = 30 kilograms	220 pounds = 100 kilograms
88 pounds = 40 kilograms	242 pounds = 110 kilograms

**PHTHALYLSULFATHIAZOLE.**—**Sulfathalidine.**—**Sharp & Dohme.**—2-(N-4-phthalyl-sulfanilamido) thiazole. The structural formula may be represented as follows:



Phthalylsulfathiazole may be prepared by the condensation of sulfathiazole with phthalic anhydrid.

For tests and standards, see Section B.

*Actions and Uses.*—Phthalylsulfathiazole is a derivative of sulfathiazole closely related to succinylsulfathiazole used for the oral treatment of infection in the intestinal tract. Unlike the latter, however, it is not recommended for acute bacillary dysentery or elimination of the carrier state. It is used in the management of inflammatory disease of the intestinal tract and for the reduction of coliform bacteria prior to operative procedures involving surgery of the small intestine or colon. There is clinical evidence to warrant its use as an adjunct to other measures in the control of both acute and chronic ulcerative colitis and regional ileitis.

Phthalylsulfathiazole is absorbed to the extent of only about 5 per cent and rarely reaches a concentration in the blood of

more than 1.5 mg. per 100 cc. with doses usually prescribed. This proportion is excreted by the kidneys, mostly conjugated, which forms soluble salts in acid urine. The possibility of crystalluria is therefore remote. No toxic manifestations have been observed with therapeutic doses except where sensitivity to sulfonamides was previously acquired.

**Dosage.**—Orally, in tablet form, from 0.05 to 0.1 Gm. per kilogram of body weight daily. This is given in equally divided doses at intervals of four, six or eight hours, depending on the total dose to be administered. The average daily adult dose is provided by eight to twelve 0.5 Gm. tablets and should not exceed 8 Gm. Smaller doses, as indicated by response, may be continued for initial periods up to eight weeks or even longer for the management of ulcerative colitis. As a preliminary adjunct to intestinal surgery, an initial dose of 0.125 Gm. per kilogram followed by the same amount daily in divided doses given at equal intervals, comprising three, four or six doses per day, is given for a period of three to five days prior to operation.

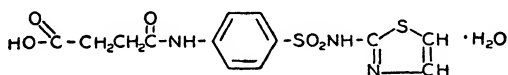
SHARP & DOHME, INC.

**Tablets Sulfathalidine: 0.5 Gm.**

U. S. patents 2,324,013 and 2,324,015. U. S. trademark, registered.

**SUCCINYLSULFATHIAZOLE-U. S. P.**—Sulfasuxidine-Sharp & Dohme.—2-(N<sup>4</sup>-succinylsulfanilamido)thiazole monohydrate.—2-(*p*-succinylaminobenzene-sulfonamido)thiazole monohydrate.—“When dried at 100 C. for 4 hours, contains not less than 99 per cent of C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O<sub>5</sub>S<sub>2</sub>.”—U. S. P.

Succinylsulfathiazole possesses the following structural formula:



For description and standards see the U. S. Pharmacopeia under Succinylsulfathiazole and Succinylsulfathiazole Tablets.

**Actions and Uses.**—While succinylsulfathiazole has some resemblance to sulfathiazole, animal experiments show it to have low toxicity and to be poorly absorbed from the intestinal tract. Thus, it has been proposed for use as an intestinal bacteriostatic agent particularly with reference to gram negative organisms. Succinylsulfathiazole, while used in the intestinal tract for its local bacteriostatic effect, appears to differ from sulfaguanidine in toxicity—succinylsulfathiazole being less toxic. It has been proposed for use in preoperative preparation and post-operative treatment of patients requiring surgical procedure on the intestinal tract, such as operations for ulcerative carcinoma of the rectum, carcinoma of the colon, fecal fistulae, ileostomy, tumor of the cecum, etc. It is valuable in the treatment of acute

bacillary dysentery and of carriers of dysentery bacilli. It also may be used for prophylaxis of dysentery.

**Dosage.**—Preoperative, initially, 0.25 Gm. per kilo of body weight by mouth, followed by a maintenance dose of 0.25 Gm. per kilo daily in six equal portions at four hour intervals. Postoperative, 0.25 Gm. per kilo daily for one or two weeks, depending on the postoperative condition. Postoperative administration should be begun as soon as the patient can take an ounce of water without undue nausea.

SHARP & DOHME, INC.

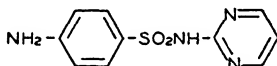
**Sulfasuxidine (Powder):** 115 Gm. and 450 Gm. glass jars.

**Tablets Sulfasuxidine:** 0.5 Gm.

U. S. patents 2,324,013 and 2,324,014 (July 13, 1943; expires 1960).  
U. S. trademark No. 394,111.

**SULFADIAZINE-U. S. P.**—2-Sulfanilamidopyrimidine.—2-Sulfanilyl aminopyrimidine.—*p*-amino-N-2-pyrimidyl benzene sulfonamide.—“When dried at 100 C. for four hours, contains not less than 99 per cent of  $C_{10}H_{10}N_4O_2S$ .”—U. S. P.

Sulfadiazine has the following structural formula:



For description and standards see the U. S. Pharmacopeia under Sulfadiazine and Sulfadiazine Tablets.

**Clinical Pharmacology.**—Sulfadiazine resembles sulfapyridine in certain of its pharmacologic effects. When the drug is administered by the oral route its rate of absorption from the gastrointestinal tract is slower and, in general, less complete than that of sulfathiazole or sulfanilamide. Sulfadiazine is, as a rule, conjugated to the acetylated form in a lesser degree in the blood and tissues than is sulfanilamide or sulfathiazole. It does not pass into the body water as readily as does sulfathiazole or sulfanilamide, but it does pass into the cerebrospinal fluid in about the same manner as does sulfanilamide. The drug passes into pleural and abdominal fluids in concentrations of one half to four fifths of those noted in the blood and penetrates the red cells with ease.

It is excreted quite readily by the kidneys, in respect both to the drug itself and to its acetylated fraction. Relatively high concentrations of sulfadiazine are easily obtained in the blood of patients to whom the drug is administered, because it is not evenly distributed in the tissues of the body. If kidney function is impaired, the excretion of sulfadiazine will be reduced and the drug will accumulate in the blood and tissues. The excretion of the drug is generally complete within 48 hours after the administration of a single dose of the compound, and in the urine

less sulfadiazine is found in the conjugated form than has been noted with sulfanilamide or sulfathiazole.

*Toxicity.*—The toxic manifestations noted in the course of sulfadiazine therapy are similar to those noted previously in the course of therapy with the other sulfonamide drugs. They are generally unpredictable in their occurrence and are generally the result of an idiosyncrasy to the drug.

Sulfadiazine causes fewer toxic reactions than do sulfanilamide or sulfathiazole. Nausea, vomiting and dizziness are uncommon. Mental disturbances and psychoses have been described. Peripheral neuritis has not been reported. Cyanosis is rare and acidosis does not occur. Fever and rashes due to the drug are less common than with the other sulfonamide drugs, except sulfaguanidine. Patients receiving sulfadiazine should be kept out of the sun. Injection of the conjunctivas and scleras has been noted. Hepatitis has been rare, but leukopenia with granulocytopenia has been observed early and late in the course of the therapy. Acute agranulocytosis has been noted rarely, occurring during the third week or later of therapy with this drug. Severe hemolytic anemias are rare. Microscopic and gross hematuria have been noted, and oliguria and anuria with azotemia have been observed. It is probable that the mechanism responsible for these renal disturbances is the same as that which has been noted previously as producing such complications in the course of sulfapyridine or sulfathiazole therapy. It is important in the course of therapy to keep the urinary output at not less than 1,000 cc. daily. When fever, rash, hepatitis, granulocytopenia, acute hemolytic anemia, agranulocytosis, hematuria with oliguria, anuria, injection of the scleras and conjunctivas or other serious toxic manifestations occur, the drug should be stopped and fluids forced in order that sulfadiazine may be eliminated from the body as rapidly as possible.

*Dosage.*—Sulfadiazine is poorly soluble and hence must be administered by the oral route. In adults suffering from pneumococcic pneumonia, severe hemolytic streptococcus infections, severe staphylococcic infections or meningococcic meningitis, the initial dose should be based on 0.10 Gm. per kilogram of body weight. Then, if the patient is suffering from pneumococcic pneumonia, 1.0 Gm. should be given every four hours day and night until the temperature has been normal for seventy-two hours. The drug may then be stopped. In severe streptococcic, staphylococcic and meningococcic infections, subsequent doses after the initial doses is 1.0 to 1.5 Gm. every four hours day and night until the temperature has been normal for from five to seven days. At this time the drug may be either stopped or continued in smaller doses until the complete recovery of the patient is assured.

In children suffering from pneumonia the initial oral dose should be based on 0.10 to 0.15 Gm. per kilogram of body weight, and subsequent doses should be one fourth of the initial dose given at intervals of six hours until the temperature has been

normal for at least forty-eight hours. In severe streptococcic, staphylococcic or meningococcic infections in children the drug should be continued until five to seven days of normal temperature have elapsed. Then it may be discontinued or if considered necessary, continued in smaller doses until a cure is effected.

In mild or moderately severe hemolytic streptococcus infections, an initial oral dose of 0.05 Gm. per kilogram of body weight, followed by one-third of the initial dose given every four hours day and night by mouth until the temperature has been normal for three to five days, has been suggested as a satisfactory dosage schedule. All of the above dosages should be controlled if possible by determination of the concentration of the drug in the blood at frequent intervals (see Bratton and Marshall method under Determination of the Sulfonamides in Body Fluids). In severe streptococcic, staphylococcic, meningococcic or Friedländer's bacillus infections it is necessary during the febrile period to obtain and maintain concentrations of approximately 15 mg. of sulfadiazine per hundred cubic centimeters in the blood of the patients. It is rarely necessary or advisable to attempt knowingly to exceed this concentration of the drug in the blood. In mild or moderately severe streptococcic infections, concentrations of the drug in the blood of 5 to 10 mg. per hundred cubic centimeters are usually satisfactory. In acute gonococcic urethritis in adults, the initial dose is 4.0 grams; this to be followed by 1.0 grams every six hours for 5 days.

\*The incidence of oliguria, hematuria and anuria following sulfadiazine therapy may prove to be great under conditions where the output of urine cannot be maintained above 600 or 800 cc. per day, as in tropical climates or where a shortage of water exists. It is recommended that under conditions where such complications are being encountered the medical officers shall administer an initial dose of 4 grams of sodium bicarbonate together with an initial dose of sulfadiazine, and shall follow this with 2 grams of sodium bicarbonate every four hours regardless of the dosage of sulfadiazine being employed. In the management of complications resulting from the toxic action of sulfadiazine on the kidneys, the administration of even larger doses of alkali, such as 3 or 4 grams every four hours, may be helpful.

ABBOTT LABORATORIES

**Sulfadiazine Sodium (*Sterile Powder*):** 5 Gm. ampuls.

**Tablets Sulfadiazine:** 0.5 Gm.

AMERICAN PHARMACEUTICAL Co., INC.

**Tablets Sulfadiazine:** 0.5 Gm.

BUFFINGTON'S, INC.

**Tablets Sulfadiazine:** 0.5 Gm.



COLE CHEMICAL CO.

Tablets Sulfadiazine: 0.5 Gm.

FLINT, EATON & CO.

Tablets Sulfadiazine: 0.5 Gm.

THE HARROWER LABORATORY, INC.

Tablets Sulfadiazine: 0.5 Gm.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

Sulfadiazine (*Powder*): 113 Gm. and 453 Gm. packages.

Tablets Sulfadiazine: 0.5 Gm.

ELI LILLY & CO.

Tablets Sulfadiazine: 65 mg. and 0.5 Gm.

MCNEIL LABORATORIES

Liquoid Sulfadiazine: 120 cc. and 480 cc. bottles.

Tablets Sulfadiazine: 0.5 Gm.

THE WM. S. MERRELL COMPANY

Tablets Sulfadiazine: 0.5 Gm.

E. S. MILLER LABORATORIES, INC.

Tablets Sulfadiazine: 0.5 Gm.

PARKE, DAVIS & COMPANY

Tablets Sulfadiazine: 0.5 Gm.

WILLIAM H. RORER, INC.

Tablets Sulfadiazine: 0.5 Gm.

SHARP & DOHME, INC.

Tablets Sulfadiazine: 0.5 Gm.

CARROLL DUNHAM SMITH PHARMACAL CO.

Sulfadiazine Tablets: 0.5 Gm.

SMITH-DORSEY COMPANY

Tablets Sulfadiazine: 0.1 Gm. and 0.5 Gm.

E. R. SQUIBB & SONS

Tablets Sulfadiazine: 0.5 Gm.

THE UPJOHN COMPANY

Tablets Sulfadiazine: 0.5 Gm.

THE VALE CHEMICAL CO., INC.

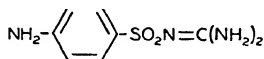
Tablets Sulfadiazine: 0.5 Gm.

WINTHROP-STEARNs, INC.

Tablets Sulfadiazine: 0.5 Gm.

**SULFAGUANIDINE-U. S. P.**—Sulfanilylguanidine monohydrate. — *p*-Aminobenzenesulfonylguanidine monohydrate. — “When dried at 105 C. for 4 hours, contains not less than 99 per cent of  $C_7H_{10}N_4O_2S$ .”—U. S. P.

Sulfaguanidine has the following structural formula:



For description and standards see the U. S. Pharmacopeia under Sulfaguanidine and Sulfaguanidine Tablets.

*Actions and Uses.*—The development of sulfaguanidine represented a new concept in bacterial chemotherapy, namely that a sulfonamide drug could be given by mouth and be quite soluble in the intestinal contents, while at the same time it would be poorly absorbed from the gastrointestinal tract, thus permitting the drug to exert its bacteriostatic and bactericidal action locally in the gastrointestinal tract.

The proper use of this drug demands that the physician shall use optimal doses spaced at such intervals as will give rise to high concentration of the drug in the stool with possibilities for minimal absorption from the gastrointestinal tract. In actual practice, one finds that when the drug is properly administered the concentrations of sulfaguanidine in the blood rarely exceed 5 mg. per hundred cubic centimeters.

On the basis of accumulated evidence the Council recognizes claims for the prophylactic use of sulfaguanidine as well as other sulfonamides in dysentery.

Sulfaguanidine is one of the least toxic of all commonly used sulfonamide drugs but nausea with vomiting, drug rash, drug fever and other types of idiosyncrasy are not uncommon. If toxic reactions occur, the drug should be stopped and fluids forced, and enemas given to eliminate the drug from the body as soon as possible.

*Dosage.*—In bacillary dysentery the initial dose by mouth is 0.05 Gm. per kilogram of body weight followed by a maintenance dose of 0.05 Gm. per kilogram every four hours day and night until the number of stools is five or less daily; then 0.05 Gm. per kilogram every eight hours for at least three days. If improvement does not occur within seven days it is unlikely that the drug will be effective on further administration. It is generally not considered wise to continue the drug for a period of more than fourteen days.

When sulfaguanidine is being used as a prophylactic agent prior to operations on the colon, the recommended dosage is 0.05 Gm. per kilogram of body weight by mouth every eight hours day and night for five days before the operation. Then, as soon as

possible after the operation, the drug should be started by mouth in the same dosage and continued for seven days. It is not, as a rule, necessary to continue the drug longer. It is recommended that the total period of dosage should not exceed fourteen days.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Sulfaguanidine (Powder):** bulk.

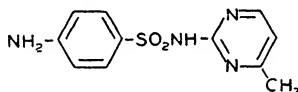
**Tablets Sulfaguanidine:** 0.5 Gm.

E. R. SQUIBB & SONS

**Tablets Sulfaguanidine:** 0.5 Gm.

**SULFAMERAZINE-U. S. P.**—Sulfamethyldiazine.—4-Methyl-2-sulfanilamidopyrimidine.—4-Methyl-2-sulfanilylamino-pyrimidine.—*p*-Amino-*N*-2-(4-methylpyrimidyl) benzenesulfonamide.—“When dried at 100 C. for 4 hours, contains not less than 99 per cent of  $C_{11}H_{12}N_4O_2S$ .”—U. S. P.

Sulfamerazine has the following structural formula:



For description and standards see the U. S. Pharmacopeia under Sulfamerazine and Sulfamerazine Tablets.

**Actions and Uses.**—The oral administration of equal doses of sulfamerazine and sulfadiazine produces in the blood a greater sulfonamide concentration of sulfamerazine than of sulfadiazine. In fact, comparable blood concentrations are obtained with approximately one-half the amount of sulfamerazine as is required of sulfadiazine. Sulfamerazine is more rapidly and more completely absorbed from the gastrointestinal tract but is excreted more slowly than sulfadiazine. Thus it may be given in smaller amounts and less frequently. This drug penetrates cerebrospinal, pleura and peritoneal fluids; the concentration of free drug in cerebrospinal fluid is approximately 50 per cent of that in serum.

The acetylated form of sulfamerazine is more soluble in urine at pH 7 or less than either the free or acetylated forms of sulfadiazine, and free sulfamerazine is more soluble than sulfadiazine in neutral or acid urine. The formation of drug concretions and renal parenchymal injury seems to be less likely to occur with sulfamerazine than with sulfadiazine if equal blood concentrations of the drug are maintained. Animal experiments suggest that the two drugs otherwise have about the same degree of toxicity but further clinical investigations in humans remain to be done to reveal the true toxicity status of sulfamerazine.

Sulfamerazine may be used in the treatment of pneumococcal, streptococcal, meningococcal and gonococcal infections.

*Dosage.*—In the treatment of acute pneumococcic, streptococcic, and meningococcic infections the maintenance of a concentration of sulfamerazine in the blood of 10 to 15 mg. of the drug per 100 cc. of blood will usually be sufficient. Blood serum concentrations of this magnitude may be attained within four hours by the oral administration of 3 or 4 Gm. of sulfamerazine as an initial dose, followed by 1.0 Gm. every eight hours. This dosage should be continued for seventy-two hours after the temperature, pulse and respiration rates return to normal.

For infants under six months of age, 0.5 Gm. initial dose and 0.25 Gm. every twelve hours thereafter; infants six months to three years, 1.0 Gm. initial dose and 0.5 Gm. every twelve hours; children three to ten years, 1.5 Gm. initial dose and 1.0 Gm. every twelve hours. In very severe infections the dosage may be increased by 50 per cent.

In the treatment of pneumococcic infections, type-specific antiserum may be administered, unless contraindicated, if the response of the patient to the drug alone is not adequate within 18 to 24 hours.

As in the case of the other sulfonamides, the appearance of toxic symptoms should be an indication for the cessation of all treatment with this drug.

ABBOTT LABORATORIES

Tablets Sulfamerazine: 0.5 Gm.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

Sulfamerazine (*Unsterile Powder*): 113 Gm. and 454 Gm. packages.

Tablets Sulfamerazine: 0.5 Gm.

ELI LILLY & CO.

Tablets Sulfamerazine: 0.5 Gm.

PARKE, DAVIS & COMPANY

Tablets Sulfamerazine: 0.5 Gm.

SHARP & DOHME, INC.

Sulfamerazine (*Unsterile Powder*): Bulk, 114 Gm.

Sulfamerazine Chemical Reagent (*Powder*): 1 Gm. vial

Tablets Sulfamerazine: 0.5 Gm.

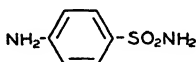
E. R. SQUIBB & SONS

Tablets Sulfamerazine: 0.5 Gm.

THE UPJOHN COMPANY

Tablets Sulfamerazine: 0.5 Gm.

**SULFANILAMIDE-U. S. P.**—*p*-Amino-benzene-sulfonamide.—The amide of sulfanilic acid. "When dried at 100 C. for 4 hours, contains not less than 99 per cent of  $C_6H_8O_2N_2S$ ." U. S. P. Sulfanilamide has the following structural formula:



For description and standards see the U. S. Pharmacopeia under Sulfanilamide and Sulfanilamide Tablets.

**Actions and Uses.**—Sulfanilamide when administered by mouth is readily absorbed from the gastrointestinal tract. It is probable that, following a single peroral dose, absorption is practically complete within four hours. The drug is evenly distributed in all body tissues with the exception of the brain, fat and bone. In patients with normal renal function, from 10 to 20 per cent of the circulating sulfanilamide is present in the acetylated or conjugated form. The drug is almost totally absorbed and is readily excreted by the normal kidneys. In the urine ordinarily from one third to one half of the excreted sulfanilamide exists as the acetylated fraction.

Many patients receiving sulfanilamide will have signs and symptoms of central nervous system disturbances such as headache, dizziness, nausea, vomiting, mild depressions or elations and in a few instances, severe toxic psychoses. Because of these toxic manifestations, patients who are receiving the drug should be warned against driving automobiles, piloting or riding in airplanes and doing any heavy or dangerous work in which a spell of dizziness might result in a serious accident. Practically all individuals who receive therapeutic doses of the drug develop some degree of cyanosis, generally apparent in the lips and nail beds, but in some cases suffusing the entire integument. The exact mode of production of this cyanosis is unknown, although in many instances it is due, at least in part, to the production of methemoglobin in the blood. It is not, in the opinion of most observers, a serious complication and rarely serves as an indication that treatment should be discontinued. Drug fever, which commonly occurs between the fifth and ninth days of therapy, is a not infrequent toxic manifestation. Rashes, which may vary in their type and which may be accompanied by fever, are also not infrequently seen in the course of sulfanilamide therapy. As these rashes are sometimes the result of a photosensitization of the skin, it is probably best for patients who are receiving sulfanilamide to keep out of the sun, and they should not receive ultraviolet irradiation.

Acidosis may be produced by the drug in certain individuals. This is probably brought about by the action of sulfanilamide in inhibiting the enzyme carbonic anhydrase. The routine, concurrent use of sodium bicarbonate generally prevents this complication of drug therapy. Hepatitis, accompanied by jaundice and,

in a few instances, ending fatally, is one of the rarer complications of sulfanilamide therapy. Acute hemolytic anemia occurring from the first to the twenty-first day of therapy, is not uncommon and is noted more frequently in Negro patients than in white patients. A severe leukopenia may occur at any time during the course of therapy, and granulocytopenia has been described not uncommonly as a toxic manifestation. The most common time for the appearance of true agranulocytosis is between the fourteenth and fortieth days of therapy. During this period white blood cell counts should be done at least every two days. In patients who have a decrease in renal function the normal excretion of the drug is impaired, and an accumulation of sulfanilamide in the blood and tissues of the patient may occur if care is not taken in regulating the dosage of the drug.

As far as is known, practically all other drugs may be prescribed concurrently with sulfanilamide.

*Dosage.*—The dose of sulfanilamide depends on the type and severity of the infection. It is suggested that in cases of serious infection an initial peroral dose of 0.1 Gm. per kilogram of body weight be administered, this to be followed by doses of the drug of one-sixth the amount of the initial dose given at four hour intervals day and night until the temperature has been normal for seventy-two hours. Then the dose of the drug may be gradually decreased until complete convalescence is established. It is to be remembered that the main index for the control of therapy with this drug should not be the dose of the drug which has been prescribed but rather the concentrations of sulfanilamide that are being obtained in the blood or other tissue fluids. It is usually advisable to continue therapy for a few days after clinical recovery has taken place in order to avoid relapses. Patients who cannot take the drug by mouth may be given subcutaneous injections of a 1 per cent solution of sulfanilamide made up in isotonic solutions of sodium chloride or, better still, in one-sixth molar sodium racemic lactate solutions. The same total dosage may be employed for parenteral as for oral administration, but the injections should be given at intervals of from six to eight hours.

ABBOTT LABORATORIES

**Sulfanilamide (*Crystals*):** 1.0 Gm. and 4.0 Gm. ampuls.

**Tablets Sulfanilamide:** 0.324 Gm. and 0.5 Gm.

AMERICAN PHARMACEUTICAL CO., INC.

**Sulfanilamide (*Powder*):** 28.35 Gm., 113.4 Gm. and 453.6 Gm. packages.

**Tablets Sulfanilamide:** 0.324 Gm. and 0.486 Gm.

GEORGE A. BREON & COMPANY, INC.

**Tablets Sulfanilamide:** 0.324 Gm.

CIBA PHARMACEUTICAL PRODUCTS, INC.

**Tablets Sulfanilamide:** 0.5 Gm.

THE DRUG PRODUCTS CO., INC.

**Pulvoids Sulfanilamide:** 0.324 Gm.

ENDO PRODUCTS, INC.

**Tablets Sulfanilamide:** 0.324 Gm. and 0.5 Gm.

FLINT, EATON & COMPANY

**Tablets Sulfanilamide:** 65 mg., 0.25 Gm., 0.324 Gm. and 0.5 Gm.

GANE AND INGRAM, INC.

**Sulfanilamide (*Powder*):** bulk.

HORTON & CONVERSE

**Tablets Sulfanilamide:** 0.324 Gm.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Sulfanilamide (*Powder*):** 113 Gm. and 453 Gm. packages.

**Tablets Sulfanilamide:** 0.324 Gm.

THE MALTBIE CHEMICAL COMPANY

**Tablets Sulfanilamide:** 0.324 Gm.

MERCK & Co., INC.

**Sulfanilamide (*Powder*):** bulk.

THE WM. S. MERRELL COMPANY

**Tablets Sulfanilamide:** 0.324 Gm.

E. S. MILLER LABORATORIES, INC.

**Tablets Sulfanilamide:** 0.324 Gm.

NATIONAL DRUG COMPANY

**Tablets Sulfanilamide:** 65 mg., and 0.325 Gm.

PARKE, DAVIS & COMPANY

**Tablets Sulfanilamide:** 0.324 Gm. and 0.5 Gm.

PITMAN-MOORE CO., DIVISION OF ALLIED LABORATORIES, INC.

**Tablets Sulfanilamide:** 0.324 Gm.

SCHIEFFELIN & Co.

**Tablets Sulfanilamide:** 0.5 Gm.

SHARP & DOHME, INC.

**Tablets Sulfanilamide:** 0.324 Gm. and 0.5 Gm.

CARROLL DUNHAM SMITH PHARMACAL CO.

**Tablets Sulfanilamide:** 0.324 Gm.

## SMITH-DORSEY COMPANY

Tablets Sulfanilamide: 0.162 Gm., 0.324 Gm. and 0.5 Gm.

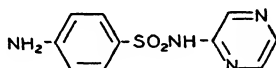
## THE UPJOHN COMPANY

Tablets Sulfanilamide: 65 mg., 0.324 Gm. and 0.5 Gm.

## WARREN-TEED PRODUCTS COMPANY

Tablets Sulfanilamide: 0.33 Gm.

**SULFAPYRAZINE.** — 2-Sulfanilamidopyrazine. — 2-Sulfanilylaminopyrazine. — *p*-Amino-N-2-pyrazinylbenzenesulfonamide. Sulfapyrazine has the following structural formula:



For tests and standards, see Section B.

**Actions and Uses.**—Sulfapyrazine appears to have a low order of toxicity in experimental animals. Although renal damage has been shown in adults, this reaction is not unlike that caused by other sulfonamides. Other reactions may be blood dyscrasias, drug fever, rash, nausea and vomiting (although this occurs less frequently than with other sulfonamides). Because the substance is absorbed and excreted rather slowly, high blood levels are not obtained with single large oral doses; dosages of one gram every four or six hours will provide adequate levels with this concentration remaining fairly constant over considerable periods of time. The drug is secreted in the cerebrospinal fluid and reaches concentrations of about one-half to two-thirds of blood level within 12 hours following intravenous administration of sulfapyrazine sodium. It is secreted also in other body fluids. It has a low degree of conjugation to acetyl sulfapyrazine.

Sulfapyrazine is probably as effective as sulfadiazine in the treatment of pneumococcal, hemolytic streptococcal and *B. coli* infections. Further it appears to be effective against *Shigella paradysenteriae*, even when these strains are resistant to other sulfonamides, and in the presence of meningococcic meningitis.

**Dosage.**—Low blood levels commonly follow administration of sulfapyrazine and often are effective. The usual dosage, however, produces concentrations from 5 to 12 mg. per 100 cc. of blood.

Initial dose for adults is 2 to 4 grams, followed by 1 gram doses at four to six hour intervals. Treatment should be continued until the temperature, pulse and respiration have been normal for three days. Infants and children should receive about 130 mg. of the drug per kilo of body weight. In general, infants under six months of age may receive 0.5 Gm. as an initial dose and 0.25 Gm. every six hours thereafter; children six months to three years, 1.0 gram initial dose, 0.5 Gm. every six hours; children three to ten years, 2.0 Gm. initial dose and

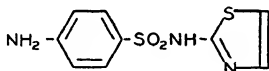


1.0 Gm. every six hours. In very severe infections the dose may be increased by 50 per cent.

MEAD JOHNSON & COMPANY

Tablets Sulfapyrazine: 0.5 Gm.

**SULFATHIAZOLE-U. S. P.**—"When dried at 100 C. for 4 hours, contains not less than 99 per cent of  $C_9H_9N_3O_2S_2$ ."—*U. S. P.* Sulfathiazole has the following structural formula:



For description and standards see the U. S. Pharmacopeia under Sulfathiazole and Sulfathiazole Tablets.

*Actions and Uses.*—Sulfathiazole resembles sulfanilamide in certain of its pharmacologic effects. In most patients it is rapidly absorbed when administered by mouth, maximum concentrations of the drug in the blood being obtained in two to three hours after the administration of a single dose. It is fairly evenly distributed throughout most of the body tissues with the exception that it does not pass readily into the spinal fluid. In the tissues a certain proportion of the drug is conjugated to the therapeutically inactive acetyl derivative. The degree of conjugation is, as a rule, slightly greater than that noted for sulfanilamide but generally less than that for sulfapyridine. It is excreted rapidly by the kidneys, and because of this it is sometimes difficult to maintain adequate concentrations of the drug in the blood and tissues. The rapid excretion of this drug is probably responsible for its relatively low degree of conjugation. If kidney function is impaired, the excretion of sulfathiazole will be reduced and the drug will accumulate in the blood and tissues.

In the urine considerably less sulfathiazole is found in the conjugated form than has been generally noted for either sulfanilamide or sulfapyridine. The excretion of the drug is generally almost complete within twenty-four hours after the administration of a single dose of the compound.

The toxic manifestations noted in the course of sulfathiazole therapy are similar to those previously noted in the course of therapy with other sulfonamides. These untoward effects are unpredictable in their occurrence and are considered to be the result of an idiosyncrasy to the drug.

Sulfathiazole causes less nausea, vomiting and dizziness than does sulfapyridine; mental disturbances or psychoses are uncommon. Questionable so-called peripheral neuritis has been reported. Cyanosis is generally mild if present, and acidosis has been noted. Sulfathiazole produces more instances of drug fever and drug rash than any of the other sulfonamide compounds in common use. These toxic manifestations generally occur between the fifth and ninth days of treatment but may occur at any period.

Urticarial or nodular rashes resembling erythema nodosum are often seen. Patients receiving the drug should be kept out of the sun.

Hepatitis is rare. Leukopenia with granulocytopenia has been noted either early or late in the course of therapy. Acute agranulocytosis has been reported as occurring in course of therapy with this drug. Mild or severe acute hemolytic anemias are uncommonly seen. Microscopic or gross hematuria has occurred in patients who have received this drug, and anuria with azotemia has been observed. The hematuria and more severe evidence of kidney damage may be due in certain instances to the formation of acetylsulfathiazole crystals and renal calculi which block the renal tubules or even the renal pelves and ureters, but in other patients these toxic manifestations seem to result from a direct toxic reaction of the drug on the renal epithelium. Because of these renal toxic reactions it is important to keep the urinary output at not less than 1,000 cc. in the course of therapy with sulfathiazole.

A curious toxic manifestation which has not been reported in the course of therapy with other sulfonamides and which has been noted frequently in the course of sulfathiazole therapy, is the injection of the scleras and conjunctivas, which when severe may give the appearance of the disease "pink eye." Mild to severe arthralgia may accompany the fever and rashes which are produced by sulfathiazole.

When fever, rash, hepatitis, granulocytopenia, acute hemolytic anemia, hematuria with oliguria, injection of the scleras and conjunctivas or other serious toxic manifestations occur, the drug should be stopped and fluids forced in order that sulfathiazole may be eliminated from the body as rapidly as possible.

As far as is known at the present time, sulfathiazole can be used concurrently with any other drugs.

*Dosage.*—Sulfathiazole is poorly soluble and hence must be administered by the oral route. In the treatment of severe infections in adults, where the drug is indicated, the initial dose of sulfathiazole should be calculated upon the basis of 0.10 grams per kilo of body weight, up to 50 Kg. of body weight to be followed by 1 Gm. every three hours day and night until the patient's temperature has been normal for 72 hours. The drug should then be decreased gradually. In children ill with pneumococcic pneumonia the initial dose should be based on 0.15 Gm. per kilogram (up to 25 Kg. of body weight) and the total daily dose is calculated on the same basis. The total daily dose should be divided into six equal parts and administered at six hour intervals until the temperature has been normal for 36 hours. The drug should then be stopped.

It is to be remembered that surgical measures, both supportive and operative, must be used in the treatment of staphylococcic infections in conjunction with sulfathiazole whenever indicated. Surgical drainage of purulent foci is generally advised because, while the drug may halt the invasive manifestations of

staphylococcic infection, it may not by itself cure areas of localized infections, and a flare-up of the infection from such areas may occur if they are not properly drained.

It is very important to control the administration of sulfathiazole by determining its concentration in the blood of patients who are receiving it. In pneumonia, concentrations of from 4 to 6 mg. per 100 cc. of the drug in the blood should be sought.

ABBOTT LABORATORIES

**Tablets Sulfathiazole:** 0.25 Gm. and 0.5 Gm.

AMERICAN PHARMACEUTICAL CO., INC.

**Tablets Sulfathiazole:** 0.5 Gm.

GEORGE A. BREON & COMPANY, INC.

**Tablets Sulfathiazole:** 0.5 Gm.

BUFFINGTON'S, INC.

**Tablets Sulfathiazole:** 0.5 Gm. and 0.25 Gm.

CIBA PHARMACEUTICAL PRODUCTS, INC.

**Tablets Sulfathiazole:** 0.5 Gm.

COLE CHEMICAL COMPANY

**Tablets Sulfathiazole:** 0.5 Gm.

THE DRUG PRODUCTS CO., INC.

**Pulvoids Sulfathiazole:** 0.5 Gm.

ENDO PRODUCTS, INC.

**Tablets Sulfathiazole:** 0.5 Gm.

FLINT, EATON & COMPANY

**Tablets Sulfathiazole:** 0.5 Gm. and 0.25 Gm.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Sulfathiazole (Powder):** 113 Gm. and 453 Gm. packages.

**Tablets Sulfathiazole:** 0.5 Gm.

ELI LILLY AND COMPANY

**Tablets Sulfathiazole:** 65 mg., 0.25 Gm. and 0.5 Gm.

MCNEIL LABORATORIES, INC.

**Tablets Sulfathiazole:** 0.5 Gm.

THE MALTBIE CHEMICAL COMPANY

**Tablets Sulfathiazole:** 0.5 Gm.

MERCK & Co., INC.

**Sulfathiazole (*Powder*).**

**Tablets Sulfathiazole: 0.5 Gm.**

THE WM. S. MERRELL COMPANY

**Tablets Sulfathiazole: 0.5 Gm.**

E. S. MILLER LABORATORIES, INC.

**Tablets Sulfathiazole: 0.5 Gm.**

PARKE, DAVIS & COMPANY

**Tablets Sulfathiazole: 0.25 Gm. and 0.5 Gm.**

PITMAN-MOORE Co., DIVISION OF ALLIED LABORATORIES, INC.

**Tablets Sulfathiazole: 0.25 Gm. (children's) and 0.5 Gm.**

PREMO PHARMACEUTICAL LABORATORIES, INC.

**Tablets Sulfathiazole: 0.5 Gm.**

SCHIEFFELIN & Co.

**Tablets Sulfathiazole: 0.5 Gm.**

SHARP & DOHME, INC.

**Tablets Sulfathiazole: 0.5 Gm.**

CARROLL DUNHAM SMITH PHARMACAL Co.

**Tablets Sulfathiazole: 0.5 Gm.**

SMITH-DORSEY COMPANY

**Tablets Sulfathiazole: 0.5 Gm.**

E. R. SQUIBB & SONS

**Tablets Sulfathiazole: 0.5 Gm.**

THE UPJOHN COMPANY

**Tablets Sulfathiazole: 0.25 Gm. and 0.5 Gm.**

THE VALE CHEMICAL Co., INC.

**Tablets Sulfathiazole: 0.5 Gm.**

WARREN-TEED PRODUCTS COMPANY

**Tablets Sulfathiazole: 0.5 Gm.**

WINTHROP-STEARNs, INC.

**Tablets Sulfathiazole: 0.25 Gm. and 0.5 Gm.**

### ***Sulfonamide Sodium Salts***

***Clinical Pharmacology.***—Solutions of sulfonamide sodium salts in distilled water are strongly alkaline and have  $pH$  ranges of from 9 to 11. When solutions of these drugs are injected intravenously the sodium ions are promptly split off, leaving the sulfonamide compound in the circulating blood. Hence, in the final analysis, sulfonamide sodium salts represent vehicles for introducing the slightly soluble parent compounds into the body. The preferred method of administering the sodium salts of sulfonamide compounds is by the intravenous route as 5 per cent solutions in sterile distilled water or sterile isotonic sodium chloride solution. As there is a possibility that boiling or other methods of sterilization may result in the breakdown of the sodium salts, it is considered unwise and even unnecessary to attempt to sterilize 5 per cent solutions of these salts which are going to be used for intravenous therapy.

The administration of 5 per cent solutions of the sodium salts of the sulfonamide compounds by the intravenous route should be carried out carefully because these solutions, being highly alkaline, are definitely irritating to the tissues and, if they are permitted to leak outside the vein may cause necrosis of the tissues with sloughing. Solutions of such strength should never be given by the intrathecal route because of the danger of producing a chemical necrosis of the tissues. Recently it has been shown that 0.3 to 0.7 per cent solutions of the sodium salts of the sulfonamide compounds can be safely administered in saline or isotonic Ringer's solution by the subcutaneous route. However, the general use of this route is not advised unless the drugs cannot be administered by the intravenous route.

***Actions and Uses.***—The indications for the use of solutions of the sodium salts of sulfonamide compounds are those instances of severe infection in which it is desired to obtain promptly adequate blood concentrations of these drugs, or for patients who by reason of disturbances of the gastro-intestinal tract, such as vomiting, are not obtaining proper concentrations of these drugs when they are given orally and, finally, for patients in whom the absorption of these drugs is poor or their rate of conjugation is such that adequate concentrations cannot be obtained in the blood and tissues by other routes of administration.

With the exception of patients ill with severe infections, or those individuals to whom these drugs cannot be given by the oral route, it is rarely necessary to administer intravenous injections of solution of the sodium salts of the sulfonamides more than once or twice. Frequent and repeated injections of the drug are not generally advised, because such injections tend to produce thrombosis of the veins. Whenever possible, rather than continuing administration of solution of sodium salt of the sulfonamide compounds by the parenteral route, administration of the parent drug should be commenced by the oral route.

**Toxicity.**—Aside from the damage to tissues which may result from the careless administration of the sodium salts of these sulfonamides by the intravenous route, the toxic reactions noted in the course of their administration are those which are noted when the parent sulfonamide is administered by the oral route.

**SULFADIAZINE SODIUM-U. S. P.**—The sodium salt of 2-sulfanilamidopyrimidine.—“When dried at 105 C. for 4 hours, contains not less than 99 per cent of  $C_{10}H_9N_4O_2SNa$ .”—U. S. P.

For description and standards see The U. S. Pharmacopeia under Sulfadiazine Sodium.

**Actions and Uses.**—The sodium salt of sulfadiazine has the same therapeutic activities and properties as does sulfadiazine. This compound has proved to be of value in the treatment of severe hemolytic streptococcus, pneumococcic, meningococcic, staphylococcic and *Escherichia coli* tissue infections.

**Dosage.**—The usual initial dose of this drug for patients who are severely ill with infections which are susceptible to the therapeutic effects of this drug is based on 0.10 gram per kilogram of body weight, up to 50 Kg. of body weight, this being made up as a 5 per cent solution in sterile distilled water or isotonic solution of sodium chloride. Regardless of the weight of the patient, it is best not to exceed a total initial dosage of 5.0 gram of sulfadiazine sodium.

It is always advisable to attempt to continue therapy by the administration of sulfadiazine by the oral route, but, if this is impossible, subsequent doses of sulfadiazine sodium should be based on 0.03 to 0.05 Gm. of sodium sulfadiazine per kilogram of body weight, made up in a 5 per cent solution in distilled water and administered by the intravenous route at about 6 to 8 hour intervals. When solutions of sulfadiazine sodium are being used as the sole means of therapy, daily determinations of the concentration of the drug in the blood should be made in order to prevent inordinately high levels of the drug from accumulating in the blood. The suggested dosages are applicable to children as well as adults.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE Co.

**Solution Sodium Sulfadiazine 25%:** 10 cc. ampules. Each cubic centimeter contains sodium sulfadiazine 2.5 Gm. in distilled water. Sodium thiosulfate 0.1 per cent used as preservative.

SHARP & DOHME, INC.

**Solution Sodium Sulfadiazine 5%:** 50 cc. ampuls. Each 50 cubic centimeters contains sodium sulfadiazine 2.5 Gm. and distilled water q. s.

**STERILE SULFADIAZINE SODIUM-U. S. P.**—Sterile Sodium Sulfadiazine.—“When dried at 105 C. for 4 hours, contains not less than 99 per cent of  $C_{10}H_9N_4O_2SNa$ .”—U. S. P.

For description and standards see The U. S. Pharmacopeia under Sterile Sulfadiazine Sodium.

*Actions, Uses and Dosage.*—Same as for Sulfadiazine Sodium.

SHARP & DOHME, INC.

**Sodium Sulfadiazine (Sterile Powder):** 5 Gm. vials.

E. R. SQUIBB & SONS

**Sodium Sulfadiazine (Sterile Powder):** 5 Gm. vial.

**SULFAMERAZINE SODIUM-U. S. P.**—The anhydrous sodium salt of 4-methyl-2-sulfanilamidopyrimidine. —“When dried at 105 C. for 4 hours, contains not less than 99 per cent of  $C_{11}H_{11}N_4O_2SNa$ .” U. S. P.

For description and standards see The U. S. Pharmacopeia under Sulfamerazine Sodium.

*Actions and Uses.*—Sodium sulfamerazine may be used intravenously for critically ill patients who require immediate and adequate drug therapy, and for patients in whom it is difficult to obtain a satisfactory drug concentration with oral administration. However, oral administration should be begun with the intravenous administration, or immediately thereafter if possible. Intravenous treatment should be discontinued as soon as a satisfactory drug level can be maintained by oral administration.

*Dosage.*—The initial dose of sulfamerazine sodium for patients who are severely ill with infections which are susceptible to the therapeutic effects of this drug is based upon 0.05 grams per kilogram of body weight, this being made up as a 5 per cent solution in sterile distilled water or sterile isotonic solution of sodium chloride. It is always advisable to attempt to continue therapy by the administration of sulfamerazine by the oral route, but if this is impossible, subsequent doses of sulfamerazine sodium should be based on 0.025 gram of sulfamerazine sodium per kilogram of body weight, made up as a 5 per cent solution in sterile distilled water or sterile isotonic solution of sodium chloride and administered by the intravenous route at intervals of 12 hours. Frequent determination of the concentration of the drug in the blood should be made. Concentrations of the drug in the blood of more than 15 milligram per cent are undesirable, and if this concentration occurs the dosage should be reduced.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Solution Sodium Sulfamerazine 25%:** 10 cc. ampuls.

SHARP & DOHME, INC.

**Sodium Sulfamerazine (Sterile Powder):** 5 Gm. vial.

**Solution Sodium Sulfamerazine 6%:** 50 cc. ampules. Each 50 cc. contains sodium sulfamerazine 3 Gm. in distilled water.

**SULFAPYRAZINE SODIUM.**—The monohydrated sodium salt of 2-sulfanilamidopyrazine.

For tests and standards, see Section B.

*Actions and Uses.*—Sodium sulfapyrazine may be administered intravenously when oral administration of sulfapyrazine is not feasible or when there is urgent need for the establishment of adequate blood levels of the drug. Oral administration should be started, if possible, with the initial injection of the sodium salt, and intravenous administration discontinued as soon as possible. This drug should not be injected intramuscularly or intraspinally.

*Dosage.*—The initial dosage of sulfapyrazine sodium for patients who are severely ill with infections which are susceptible to the therapeutic effects of this drug is based upon 0.05 gram per kilogram of body weight, this being made up as a 5 per cent solution in sterile distilled water or sterile isotonic solution of sodium chloride. If subsequent doses of sulfapyrazine sodium are desirable, they should be based on 0.025 gram of sulfapyrazine sodium per kilogram of body weight made up as a 5 per cent solution in sterile distilled water or sterile isotonic solution of sodium chloride and administered by the intravenous route at intervals of 8 to 12 hours. Frequent determination of the concentration of the drug in the blood should be made. Concentrations of the drug in the blood of more than 15 milligram per cent are undesirable and if this concentration occurs the dosage should be reduced.

MEAD JOHNSON & COMPANY

**Sodium Sulfapyrazine (Powder):** 5 Gm. bottles.

**SULFATHIAZOLE SODIUM-U. S. P.**—Sodium 2-sulfanilamidothiazole.—Sodium 2-sulfanilylthiazole.—The sodium salt of sulfathiazole. "When dried at 100 C. for 5 hours, contains not less than 99 per cent of  $C_9H_8N_3O_2S_2 Na$ ."—U. S. P.

For description and standards see The U. S. Pharmacopeia under Sulfathiazole Sodium and Sterile Sulfathiazole Sodium.

*Actions and Uses.*—The sodium salts of sulfathiazole have the same therapeutic activities as sulfathiazole. This compound has proved to be of value in the treatment of severe pneumococcal, meningococcal, staphylococcal and gonococcal infections.

*Dosage.*—The initial dosage of sulfathiazole sodium for patients who are severely ill with infections which are susceptible to the therapeutic effects of this drug is based upon 0.10 grams per kilogram of body weight up to 50 Kg. of body weight made up as a 5 per cent solution in sterile distilled water or sterile isotonic solution of sodium chloride. If subsequent doses of sulfathiazole sodium are desirable they should be based upon 0.05 grams per kilogram of body weight made up as a 5 per cent solution in sterile distilled water or sterile isotonic solution of sodium chlo-



ride and administered by the intravenous route at intervals of 6 hours. Frequent determination of the concentration of the drug in the blood should be made and with sulfathiazole sodium, the "total" drug—as well as its "free" component should always be calculated. It is undesirable to have the concentration of the "total" drug exceed 12 milligram per cent.

ABBOTT LABORATORIES

**Sodium Sulfathiazole Anhydrous (Powder):** 5 Gm. ampuls.

LEDERLE LABORATORIES. DIVISION AMERICAN CYANAMIDE CO.

**Solution Sodium Sulfathiazole 25%: 10 cc. ampuls.**

MERCK & Co., INC.

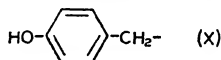
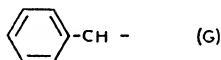
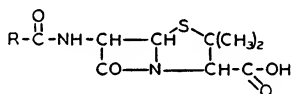
**Sodium Sulfathiazole Sesquihydrate (Powder):** 30 Gm., 113 Gm. and 453 Gm.

WINTHROP-STEARNS, INC.

**Sodium Sulfathiazole Anhydrous (Powder):** 1 Gm. ampuls and 5 Gm. bottle.

## Antibiotics

**PENICILLIN.**—An antibiotic substance, existing in several forms, that is derived from certain species of molds belonging to the genus, *Penicillium*, by extraction of cultures grown on special media. The various forms of penicillin, so far isolated, have been designated as F, G, K, and X. Their structural formulas may be represented as follows:



Amorphous mixtures have been widely employed in the form of their sodium or calcium salts. Crystalline preparations of greater purity and stability containing more than one kind of penicillin or containing chiefly penicillin G, either as the sodium or potassium salt have also been developed. Penicillin in any form is re-

quired to be certified under the regulations of the Food and Drug Administration.

Penicillin mixtures for parenteral or oral use are limited by the Food and Drug Administration to a content of not more than 30 per cent of penicillin K; topical forms are not restricted as to content. Crystalline penicillin is defined by that agency as the heat-stable crystalline (sodium or potassium) salt of one or more kinds of penicillin and must be capable of withstanding exposure to 100 C. for four days. Amorphous and crystalline mixtures are required to have a potency of not less than 500 units per milligram or when comprising at least 90 per cent of penicillin X, a potency of not less than 350 units per milligram. Crystalline preparations designated as Crystalline Penicillin G are required to contain 90 per cent of G, determined by the N-ethylpiperidine method; the sodium salt to have a potency of not less than 1500 units per milligram; the potassium salt a potency of not less than 1435 units per milligram. One unit is defined as the penicillin activity contained in 0.6 microgram of the Food and Drug Administration master standard and is approximately equivalent to the original Oxford unit. Potency is assayed by bacteriologic testing against a strain of *Staphylococcus aureus* or other suitable organisms.

Noncrystalline penicillin salts require refrigeration in the dry state and in solution, to preserve potency. Crystalline penicillin is stable up to three years in dry form without refrigeration, but in solution below pH 6.0, it is stable for only 3 days at a temperature of 8 to 14 C. Refrigerated solutions buffered to a pH of 6.0 or above retain their potency for a minimum of seven days. Tablets should be protected against moisture to prevent deterioration.

For standards of certain dosage forms of amorphous penicillin see the U. S. Pharmacopeia under Penicillin Calcium, Penicillin Sodium, Penicillin Dental Cones, Penicillin Injection in Oil and Wax, Penicillin Ointment, Penicillin Tablets and Penicillin Troches.

*Action and Uses.*—Penicillin in either the crystalline or amorphous form is chiefly effective against gram-positive bacteria, particularly against staphylococcal, streptococcal, pneumococcal, and clostridial infections, but also against gram-negative gonococcal and meningococcal infections. It is also effective in bacterial endocarditis, due to susceptible organisms, and against anthrax infection. It has been found useful in the treatment of syphilis, leptospirosis, Vincent's infection, actinomycosis and infection with *Streptobacillus moniliformis*, but its ultimate curative value in these conditions is not yet clearly defined. It has not been demonstrated that penicillin alone is of therapeutic value in the treatment of clinical diphtheria, and it should never be used for this purpose. However, current evidence indicates that the convalescent carrier state may be shortened by the concomitant use of adequate amounts of antitoxin and of at least 240,000 units of penicillin per day, for a period of not less than

twelve days, during the active clinical phase of diphtheria. Penicillin is of little value in mixed infections in which the predominating organism is gram-negative and is not effective against gram-negative bacillary infections, viral infections, most fungus infections, nonspecific inflammatory conditions, tuberculosis, amebiasis, malaria and neoplastic diseases.

Penicillin may be administered orally, parenterally by inhalation or topically. It is partially inactivated by gastric juice but chiefly because of irregular absorption from the intestine, oral administration requires the use of doses five times the amount usually recommended for injection. Oral doses should be given between meals, preferably buffered with a suitable antacid such as, sodium citrate, aluminum dihydroxy amino acetate or aluminum hydroxide. By injection, penicillin is preferably administered intramuscularly, dissolved either in sterile distilled water or isotonic solution of sodium chloride containing from 10,000 to 50,000 units per cubic centimeter. Because penicillin is rapidly excreted injections should be repeated at not less than 3 hour intervals. Penicillin (calcium or potassium) in a special vehicle of either peanut or sesame oil and white wax, U. S. P. to delay absorption exerts a more prolonged effect and may achieve adequate blood levels in concentrations of 300,000 units per cubic centimeter, if given at intervals of 12 to 24 hours. A crystalline procaine salt of penicillin G has been found to be relatively insoluble in water. One cc. of a suspension of procaine penicillin G in oil in a concentration of 300,000 units per cc. will usually provide adequate blood levels of penicillin for from 24 to 48 hours after deep intramuscular injection. Procaine penicillin G in oil is more slowly absorbed than penicillin in oil and wax, and the levels 4 hours after injection are usually lower than those following injection of the oil and wax suspension. Duration of blood levels is usually longer following injection of procaine penicillin G in oil than following injection of penicillin in oil and wax. Procaine penicillin G is no more toxic than other penicillin preparations, and intramuscular injection is reported to be virtually painless. Subcutaneous injection is subject to erratic absorption but is not painful as in the case with non-crystalline forms of the drug. In severe infections, continuous intravenous infusion of the solution containing 25 to 50 units per cubic centimeter should be administered at a uniform rate of 5,000 to 10,000 units per hour. Concentrations of 1,000 units per cubic centimeter (not to exceed a single total dose of 20,000 units) are used for intrathecal or intracisternal injection in the treatment of meningitis because penicillin from the blood stream does not appreciably penetrate the subarachnoid space. Penicillin by inhalation through the nebulizing of 25,000 to 50,000 units per cc. every three to four hours provides good blood levels and is a useful method in the treatment of chronic pulmonary infection. In some instances it has been shown to be an effective adjunct in the treatment of pneumonia. For patients who are not seriously ill and in whom the use of multiple injections are im-

practical, the aerosol treatment can be used for the injection of penicillin. Penicillin may be applied topically in powder form, in isotonic sodium chloride solution containing 250 units per cubic centimeter, or in ointment containing 500 to 1,000 units per gram. The calcium salt is also used in the form of troches for its topical effects against Vincent's stomatitis and other penicillin-susceptible infections of the mouth. The various salts are considered about equal in penicillin activity.

Penicillin is essentially nontoxic, though delayed urticarial reactions have occurred with its systemic use. Applied locally it may produce epidermal sensitivity in as many as 10 per cent of cases, particularly in patients with eczematous tendency. If used locally, the period of application should not exceed five days and renewed application after an interval should be made with great caution.

An aerosol of penicillin, made by nebulizing a solution of penicillin containing 25,000 to 50,000 units per cc., in a suitable nebulizer, has been found useful for oral inhalation in the treatment of chronic pulmonary infections due to penicillin-sensitive organisms. In patients who are not seriously ill, and in whom it would seem impractical to use multiple injections, penicillin aerosol has been shown to be effective as an adjunct in the treatment of pneumonia. Nasal inhalation of an aerosol of penicillin by means of a negative pressure device has also been shown to be clinically effective for the treatment of penicillin-susceptible infections of the paranasal sinuses. Soluble tablets are available specially suited for dissolving the drug in a nebulizer for aerosol administration, in small quantities of the milk or water formula of infants for oral administration, and in the mouth for sublingual administration when there is difficulty in swallowing.

*Dosage.*—In serious penicillin-susceptible infections, with or without bacteremia, the average dosage is 200,000 to 300,000 units per 24 hour period; in chronic pyogenic infections, as an adjunct to surgical treatment, the dosage should be from 40,000 to 80,000 units every six hours; in acute gonorrhea, doses of 30,000 units every three hours may be given to hospitalized patients. As an aerosol, 25,000 to 50,000 units per cc. should be nebulized and inhaled every three to four hours.

Penicillin in oil and wax and procaine penicillin G in oil may be administered by deep intramuscular injection. A single dose of 300,000 units once every 24 hours will usually suffice for ordinary infections due to penicillin susceptible organisms. Severe or fulminating infections, including bacterial endocarditis, should be treated with doses of 600,000 units given once or twice daily.

It should be kept in mind that inadequate dosage may create penicillin resistance to otherwise susceptible organisms and that duration of treatment should be determined in accordance with culture findings, cessation of fever or other evidence that the infection is controlled. In meningitis, endocarditis and infections complicated by abscess formation or involving serious cavities

penicillin should be administered parenterally; in acute infections with bacteremia or septicemia, parenteral administration should be continued until blood cultures become negative and the acute condition is controlled. Oral penicillin alone, should be relied upon in acute infections only when the patient responds promptly to treatment; uncomplicated gonorrhea, acute streptococcal infections of the respiratory tract, pneumococcal pneumonia, and certain mild staphylococcal infections may be treated successfully with adequate doses or oral penicillin. Against secondary infections after tonsillectomy or tooth extraction in cases with a history of rheumatic fever to rheumatic heart disease, congenital heart disease and other conditions in which secondary infections may occur, oral doses of 100,000 to 200,000 units daily in divided doses should be given from one day before to three or four days after surgery. In seronegative primary syphilis, 60,000 units should be given intramuscularly every 2 to 3 hours for a total of 3,600,000 units; for seropositive primary and early secondary syphilis, a total of 90 similar doses are given for a total of 5,400,000 units. Until more is known of its ultimate curative value, its use should be considered an adjunct and not a substitute for arseno-bismuth therapy.

#### ABBOTT LABORATORIES

**Penicillin Sodium:** Vials containing 100,000, 200,000, 500,000 and 1,000,000 units.

**Penicillin Calcium in Oil and Wax:** 300,000 units per cubic centimeter in B-D<sup>1</sup> 1 cc. glass cartridge with B-D Disposable Cartridge Syringe; and in B-D 1 cc. cartridge, with flushing fluid (benzyl alcohol 1.5 per cent in isotonic solution of sodium chloride), for use in B-D Cartridge Syringe. Calcium penicillin suspended in peanut oil containing 4.8 per cent (W/V) white wax, U. S. P.

<sup>1</sup> Trademark registered, Becton, Dickinson & Co.

**Ointment Penicillin Calcium:** 30 Gm. tubes. Each gram contains 1,000 units of penicillin calcium in white petrolatum, U. S. P.

**Ophthalmic Ointment Penicillin Calcium:** 4 Gm. tubes. Each gram contains 1,000 units of penicillin calcium in a base consisting of white petrolatum, U. S. P., 90 per cent and liquid petrolatum, U. S. P., 10 per cent.

**Tablets Penicillin Calcium:** 50,000 units with sodium citrate 0.5 Gm. as a buffer.

**Tablets Penicillin Calcium:** 100,000 units with sodium citrate 1 Gm. as a buffer.

**Troches Penicillin Calcium:** 1,000 units.

**Crystalline Penicillin G Sodium:** Vials containing 100,000, 200,000, 500,000 and 1,000,000 units.

**Crystalline Penicillin G Sodium in Oil and Wax:** 300,000 units per cubic centimeter in B-D<sup>1</sup> 1 cc. glass cartridge with B-D Disposable Cartridge Syringe. Crystalline penicillin G sodium suspended in peanut oil containing 4.8 per cent white wax U. S. P.

**Crystalline Penicillin G Potassium in Oil and Wax (*Free Flowing*):** 300,000 units per cc., 10 cc. vials. Crystalline penicillin G potassium suspended in peanut oil containing 4.8 per cent white wax U. S. P.

**Dulcet Tablets Crystalline Penicillin G Potassium (*Buffered*):** 50,000 units with calcium carbonate 0.25 Gm. as a buffer.

U. S. trademark 500,527.

BIO-RAMO DRUG CO.

**Penicillin Sodium:** 200,000 and 500,000 unit vials.

BREWER & CO., INC.

**Penicillin Sodium:** 20 cc. vials containing 100,000 and 200,000 units and combination packages of 100,000 units in 20 cc. vials packaged with a 20 cc. vial of isotonic solution of sodium chloride.

BRISTOL LABORATORIES, INC.

**Penicillin Calcium:** 20 cc. vials. 100,000 and 200,000 units.

**Penicillin Sodium:** 20 cc. vials containing 100,000 units.

**Penicillin Calcium in Oil and Wax:** 300,000 units per cubic centimeter, 10 cc. vials. Calcium penicillin suspended in peanut oil containing 4.8% (W/V) white wax, U. S. P.

**Tablets Penicillin Calcium:** 50,000 units with calcium carbonate 0.5 Gm. as a buffer.

**Crystalline Penicillin Sodium:** 20 cc. vials containing 100,000 units, 200,000 units or 500,000 units and in combination packages containing a vial of penicillin sodium and a 2 cc. vial of isotonic salt solution.

**Crystalline Penicillin G Sodium in Oil and Wax (*Free Flowing*):** 300,000 units per cc. suspended in peanut oil containing 4.8 per cent (W/V) white wax U. S. P. 1 cc. cartridges and 10 cc. vials.

BURROUGHS WELLCOME & CO., INC.

**Penicillin Sodium:** 100,000 unit bottles.

## COMMERCIAL SOLVENTS CORPORATION

**Penicillin Calcium:** 100,000 unit vials.

**Penicillin Sodium:** 100,000 unit vials.

**Crystalline Penicillin Sodium:** 200,000 and 500,000 units in 20 cc. vials.

**Penicillin G Potassium in Oil and Wax:** 300,000 units per cubic centimeter. One 1 cc. glass cartridge in package with disposable plastic syringe and needle assembly; five 1 cc. glass cartridges in package with or without permanent syringe assembly consisting of metal syringe and two stainless steel 1½ inch (3.8 cm.) 20 gage needles. Potassium penicillin G suspended in peanut oil containing 4.8 per cent white wax U. S. P.

**Crystalline Penicillin G Potassium:** 100,000, 200,000 and 500,000 units.

**Crystalline Penicillin G Sodium:** 1,000,000 units in 50 cc. vials.

**Crystalline Penicillin G Potassium in Oil and Wax:** 10 cc. and 20 cc. vials. Each cubic centimeter contains 300,000 units. Potassium penicillin suspended in peanut oil containing 4.8 per cent (W/V) white wax, U. S. P.

**Tablets Crystalline Penicillin G Potassium:** 100,000 units buffered with glycerides and sodium salts of fatty acids.

**Soluble Tablets Crystalline Penicillin G Potassium:** 50,000 units.

**Troches Crystalline Penicillin G Potassium:** 5,000 units.

**Crystalline Penicillin G Potassium:** 1,000,000 units, 50 cc. vials.

**Crystalline Penicillin G Potassium in Oil and Wax (Free Flowing):** 300,000 units per cc., 10 cc. vials.

**Crystalline Procaine Penicillin G in Oil:** 300,000 units per cc. in peanut oil, 10 cc. vials.

## HEYDEN CHEMICAL CORPORATION

**Penicillin Calcium:** 100,000 and 200,000 unit ampuls and vials.

**Penicillin Sodium:** 100,000, 200,000, 500,000 and 1,000,000 units in 2 cc. vials.

## LAKESIDE LABORATORIES, INC.

**Penicillin Sodium:** 100,000, 200,000 or 500,000 units in 20 cc. vials and 100,000 units in 20 cc. vials packaged with an accompanying 20 cc. vial of isotonic solution of sodium chloride.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Penicillin Sodium:** Vials containing 100,000 units.

**Crystalline Penicillin G Sodium (*Buffered*):** 100,000, 200,000 and 500,000 unit vials with sodium citrate U. S. P. as a buffer.

ELI LILLY & Co.

**Penicillin Sodium:** Ampuls of 100,000 and 200,000 units.

**Crystalline Penicillin G Sodium:** 20 cc. ampuls containing 100,000, 200,000, 500,000 and 1,000,000 units.

**Crystalline Penicillin G Potassium in Oil and Wax:** 300,000 units per cubic centimeter in 1 cc. glass cartridges with B-D<sup>1</sup> Disposable Cartridge Syringe and in 10 cc. ampuls. Crystalline potassium penicillin G suspended in peanut oil containing 4.8 per cent white wax U. S. P.

<sup>1</sup> Trademark registered, Becton, Dickinson & Co.

**Tablets Crystalline Penicillin G Potassium:** 50,000 and 100,000 units, with sodium citrate as a buffer.

**Crystalline Penicillin G Potassium:** 100,000, 200,000, 500,000 and 1,000,000 units, 20 cc. vials.

**Ointment Crystalline Penicillin G Potassium:** 1,000 units per gram, 28 Gm. tubes.

**Ophthalmic Ointment Crystalline Penicillin G Potassium:** 1,000 units per gram, 3.5 Gm. tubes.

**Troches Crystalline Penicillin G Potassium:** 5,000 units.

MERCK & Co., INC.

**Penicillin Calcium:** 100,000 and 200,000 unit vials.

**Penicillin Sodium:** 100,000 and 200,000 unit vials.

**Crystalline Penicillin-G Sodium:** 100,000, 200,000, and 500,000 units in 20 cc. vials.

THE WM. S. MERRELL Co.

**Penicillin Sodium:** 100,000, 200,000, 500,000 and 1,000,000 units.

**Penicillin Calcium in Oil and Wax:** 300,000 units per cubic centimeter, 10 cc. vials. Calcium penicillin suspended in peanut oil containing 4.8 per cent white wax, U. S. P.

**Crystalline Penicillin G Sodium in Oil and Wax:** 300,000 units per cubic centimeter, 10 cc. vials. Sodium penicillin G suspended in peanut oil, containing 4.8 per cent white wax, U. S. P.

PARKE, DAVIS & COMPANY

**Penicillin Sodium:** Vials containing 100,000 units.



CHAS. PFIZER & Co.

**Penicillin Calcium:** Bulk. Marketed in bottles containing approximately one billion units each.

**Penicillin Sodium:** 100,000 unit bottles.

**Crystalline Penicillin G Sodium:** 100,000, 200,000, 500,000 and 1,000,000 unit vials and bulk in bottles containing approximately 1 billion units.

**Crystalline Penicillin G Potassium:** Bottles containing 100,000, 200,000 and 500,000 units and in bulk in bottles containing approximately one billion units.

PREMO PHARMACEUTICAL LABORATORIES, INC.

**Penicillin Sodium:** Vials containing 100,000, 200,000, 500,000 and 1,000,000 unit vials.

**Penicillin Calcium in Oil and Wax:** 1 cc. syringe or 5 cc. vials, 300,000 units per cc.

**Penicillin Calcium in Oil and Wax:** 300,000 units per cc., 2 cc. and 5 cc. glass syringes and 10 cc. vials. Calcium penicillin suspended in sesame oil containing 4.8 per cent (W/V) white wax, U. S. P.

**Crystalline Penicillin Sodium:** 20 cc. vials containing 100,000 units or 200,000 units.

**Ointment Penicillin Calcium:** 28.5 Gm. tubes. Each gram contains 2,000 or 5,000 units of penicillin calcium in a base consisting of white petrolatum U. S. P. and anhydrous wool fat.

**Tablets Penicillin Calcium:** 50,000 units and 100,000 units with calcium carbonate 0.25 Gm. as a buffer.

**Troches Penicillin Calcium:** 5,000 units.

**Crystalline Penicillin Sodium in Oil and Wax:** 300,000 units per cc., 5 cc. and 10 cc. vials. Sodium penicillin suspended in sesame oil containing 4.8 per cent (W/V) white wax, U. S. P.

**Crystalline Penicillin G Sodium:** 20 cc. vials containing 100,000 units, 200,000 units, 500,000 units and 1,000,000 units.

**Nebutabs Crystalline Penicillin G Sodium:** 50,000 units. For use in the preparation of solutions for nebulization. Packaged with or without an oral nebulizer or with a nasal nebulizer. U. S. patent applied for.

**Crystalline Penicillin G Sodium in Oil and Wax:** 300,000 units per cc., 10 cc. vials. Penicillin G sodium suspended in sesame oil containing 4.8 per cent (W/V) white wax, U. S. P.

**Crystalline Penicillin G Sodium in Oil and Wax:** 300,000 units per cc., 1 cc. glass disposable syringe. Crystalline Penicillin G sodium suspended in peanut oil containing 4.8 per cent white wax U. S. P.

**Crystalline Penicillin Sodium G in Oil and Wax:** 300,000 units per cubic centimeter in 1 cc. glass disposable syringe and 5 cc. and 10 cc. vials. Crystalline sodium penicillin G suspended in sesame oil containing 4.8 per cent white wax U. S. P.

**Crystalline Penicillin G Sodium in Oil and Wax:** 300,000 units per cc. in 1 cc. glass hypodermic syringe, packed with or without plunger and needles. Crystalline penicillin G sodium suspended in sesame oil containing 4.8 per cent white wax U. S. P.

**Crystalline Penicillin G Sodium in Oil and Wax (*Free Flowing*):** 300,000 units per cc., 10 cc. vials. Crystalline penicillin G sodium suspended in peanut oil containing 4.8 per cent white wax U. S. P.

**Crystalline Penicillin G Potassium in Oil and Wax:** 300,000 units per cc., 5 cc. and 10 cc. vials suspended in peanut oil containing 4.8 per cent (W/V) white wax, U. S. P.

SCHENLEY LABORATORIES, INC.

**Penicillin Calcium:** 20 cc. vials containing 200,000 units.

**Penicillin Sodium:** 20 cc. vials containing 100,000 units, 200,000 units or 500,000 units.

**Penicillin Sodium:** 1,000,000 units in 100 cc. vials.

**Ointment Penicillin Calcium:** 28.35 Gm. tubes. Each gram contains 1,000 units of penicillin calcium in a base consisting of white petrolatum, U. S. P., 78 per cent, mineral oil 3.5 per cent, beeswax 3.5 per cent and anhydrous lanolin, U. S. P., 15 per cent.

**Ophthalmic Ointment Penicillin Calcium:** 3.54 Gm. tubes. Each gram contains 2,000 units of penicillin calcium in white petrolatum, U. S. P.

**Tablets Penicillin Calcium:** 50,000 units with calcium carbonate 0.45 Gm. as a buffer.

**Troches Penicillin Calcium:** 1,000 units.

CARROLL DUNHAM SMITH PHARMACAL CO.

**Penicillin Sodium:** 20 cc. vial containing 100,000 units, packaged with a 20 cc. vial of isotonic solution of sodium chloride.

SMITH-DORSEY COMPANY

**Penicillin Sodium:** 100,000 unit vials and 100,000 unit vials packaged with an accompanying 20 cc. vial of isotonic solution of sodium chloride.

E. R. SQUIBB & SONS

**Penicillin Sodium:** 200,000 unit vials.

**Crystalline Penicillin G Sodium:** 500,000 and 1,000,000 unit vials.

**Crystalline Penicillin G Sodium (Buffered):** 100,000 unit and 200,000 unit vials. Buffered with sodium citrate.

**Crystalline Penicillin G Sodium in Oil and Wax:** Double-cell cartridge, one cell containing 1 cc. sterile crystalline penicillin G sodium, 300,000 units, in peanut oil with bleached beeswax 4.8 per cent (W/V) and one cell containing sterile aspirating test solution with 0.5 per cent chlorobutanol. Packaged with plastic syringe, or alone for use with permanent syringe. Also available in 10 cc. vials.

**Crystalline Penicillin G Sodium in Oil and Wax (Free Flowing):** 300,000 units per cc., 10 cc. vials. Crystalline penicillin G sodium suspended in peanut oil containing 4.8 per cent white wax U. S. P.

**Ointment Penicillin Calcium:** 1,000 units per gram. 30 Gm. tubes. Penicillin calcium in a base consisting of petrolatum 40 per cent, beeswax 4 per cent, anhydrous lanolin 10 per cent and peanut oil approximately 46 per cent.

**Ointment Penicillin Calcium:** 1,000 units per gram. 15 Gm. tubes. Penicillin calcium in a base consisting of beeswax, petrolatum and anhydrous lanolin.

**Ointment Penicillin Calcium:** 1,000 units per gram. 60 Gm. tubes. Penicillin calcium in a base consisting of beeswax, peanut oil, petrolatum and wool fat.

**Ophthalmic Ointment Penicillin Calcium:** 1,000 units per gram. 3.6 Gm. tubes. Penicillin calcium in a base consisting of petrolatum 40 per cent, beeswax 4 per cent, anhydrous lanolin 10 per cent and peanut oil approximately 46 per cent.

**Tablets Penicillin G Sodium:** 50,000 units and 100,000 units with 0.5 Gm. of trisodium citrate as a buffer.

**Chewing Troches Penicillin Calcium:** 20,000 units.

**Troches Penicillin Calcium:** 5,000 units.

STERONE CHEMICAL COMPANY, INC.

**Penicillin Calcium in Oil and Wax:** 300,000 units per cc. in 1 cc. cartridges and 10 cc. vials. Calcium penicillin suspended in sesame oil containing 4.8 per cent (W/V) white wax U. S. P.

THE UPJOHN COMPANY

**Penicillin Sodium:** Vials containing 100,000 units.

**Crystalline Penicillin G Sodium:** 100,000, 200,000, 500,000 units per cc., 25 cc. vials; 1,000,000 units per cc., 50 cc. vials, and 100,000 units in single combination packages with 20 cc. vials of sterile isotonic sodium chloride solution.

**Tablets Penicillin Calcium:** 50,000 units and 100,000 units with calcium carbonate 0.26 Gm. as a buffer.

**Crystalline Penicillin G Potassium in Oil and Wax:** 300,000 units per cubic centimeter in 1 cc. cartridges with B-D<sup>1</sup> Disposable Cartridge Syringe. Potassium Penicillin suspended in peanut oil containing 4.8 per cent (W/V) white wax, U. S. P.

<sup>1</sup> Trademark registered, Becton, Dickinson & Co.

WILLIAM R. WARNER & Co., INC.

**Penicillin Sodium:** 100,000 unit ampuls.

WINTHROP-STEARNs, INC.

**Penicillin Sodium:** 100,000 or 200,000 unit vials.

**Ophthalmic Ointment Penicillin Calcium:** 3.54 Gm. tubes. Each gram contains 1,000 units of penicillin calcium in a base consisting of white petrolatum, U. S. P., 60 per cent and liquid petrolatum, U. S. P., 20 per cent and lanolin anhydrous, U. S. P., 20 per cent.

WYETH INCORPORATED

**Penicillin Calcium:** 100,000 unit vials.

**Penicillin Sodium:** 200,000 unit and 500,000 unit vials.

**Penicillin Calcium in Oil and Wax:** 300,000 units per cc. Penicillin calcium suspended in peanut oil containing 4.8 per cent white wax, U. S. P. free flowing at room temperature. Tubex of 1 cc. and vials of 10 cc.

U. S. Trademark, 406,632.

**STREPTOMYCIN.**—Streptomycin is a purified active anti-biotic principle produced by certain strains of *Streptomyces griseus* when they are grown on suitable mediums. It has the property of inhibiting the growth and of occasionally destroying certain gram-positive and gram-negative bacteria. It may be prepared as several salts, including the hydrochloride and sulfate salts, and the calcium chloride complex double salt.

It is not a pure product but is marketed as a sterile powder in airtight ampules or vials, the activity in terms of milligrams or grams of pure streptomycin base being declared on the label.

Streptomycin in dry form may be stored at room temperature, not exceeding 30° C. for periods up to one year, however, it should be stored in the original unopened container to prevent contamination and diluquescence. Solutions of streptomycin may be stored at room temperature for one week without significant loss of potency. Solutions which have been acidified or alkalized, i.e., those having a pH lower than 4 or higher than 7, are less stable. Streptomycin solutions should not be autoclaved, and only freshly prepared solutions should be used parenterally because of the potential danger of contamination. Streptomycin



vide-resistant bacillary dysentery, and other infections due to streptomycin-susceptible organisms may be treated with this agent.

Experience with streptomycin in the treatment of undulant fever, bacillary dysentery and typhoid has been disappointing, and failure of therapy has been the rule. Until further work elucidates the place of streptomycin in these infections, its use cannot be recommended.

Although streptomycin shows promising results in the therapy of tuberculous infections in guinea pigs, the clinical experience in human infections has not been sufficiently large to delineate its precise role in the control of all forms of human tuberculosis. Striking results have been obtained in certain patients with miliary and tuberculous meningitis. In these cases streptomycin is mandatory. Excellent results have been obtained in patients with tuberculous sinuses—and in patients with mucous membrane and laryngeal tuberculosis. The results have also been impressive in tuberculous enteritis and peritonitis. In renal tuberculosis, the dysuria and frequency are often reduced, and the capacity of the bladder increased. The pyuria decreases, the number of organisms decrease although complete cure of the process is infrequent. In pulmonary tuberculosis at least 50 to 80 per cent of patients with predominately exudative lesions show improvement.

Streptomycin is capable of producing side reactions of varying severity. The most serious toxic effect is its neurotoxic action on the eighth nerve, which may occur in about 10 per cent of patients treated with large doses (3 to 4 Gm. daily) over periods of several weeks to months. This is characterized by vertigo, tinnitus, disturbance of equilibrium and diminished auditory acuity. On cessation of therapy, partial recovery of eighth nerve function is the rule, although this recovery is slow, and vestibular function appears to be permanently impaired although compensation occurs. Minor toxic effects include skin rashes, mild malaise, muscular aching and drug fever.

*Dosage.*—For intramuscular injection, the powder should be dissolved in sterile, pyrogen-free distilled water or isotonic solution of sodium chloride to give a concentration of from 100 to 200 mg. of streptomycin base per cubic centimeter. For subcutaneous injection, more dilute solutions are recommended. If the drug is administered by intravenous drip, 1 to 2 Gm. dissolved in a liter of isotonic solution of sodium chloride may be administered at a rate of about 25 drops per minute. For intrathecal administration, 10 to 20 mg. per cubic centimeter in isotonic sodium chloride solution should be used. For topical application, solutions containing 25 to 50 mg. per cubic centimeter may be used.

The dosage of streptomycin should be governed by the susceptibility of the organism responsible for the infection. In severe fulminating infections, doses of 2 to 4 Gm. daily may be necessary, given in divided doses, parenterally, every six hours.

In less severe infections, and with highly susceptible organisms, daily doses of from 1 to 2 Gm. may be sufficient. Treatment should be continued for at least 48 to 72 hours after the temperature returns to normal and all signs of infection have disappeared. In all types of tuberculosis, excepting the miliary and meningeal forms, 1 Gm. of streptomycin is given daily intramuscularly in two doses of 0.5 Gm. each at 12 hour intervals for a total of 120 days as an adjunct to other forms of therapy. In acute miliary tuberculosis and tuberculous meningitis, intramuscular doses of 2.0 Gm. or more daily are given. In the later instance, the intrathecal injection of 50 mg. of streptomycin every one or two days may be used in conjunction with the intramuscular administration of streptomycin.

It is important to give sufficiently large doses to inhibit or kill the infecting organisms quickly, since the development of "fastness" to streptomycin is common and may occur rapidly. Inadequate dosage predisposes to the development of resistant strains of the organisms.

#### ABBOTT LABORATORIES

**Streptomycin Sulfate:** Vials containing streptomycin sulfate equivalent in activity to 1 Gm. of streptomycin base (one million units).

#### MERCK & Co., INC.

**Streptomycin Calcium Chloride Complex:** Vials containing streptomycin calcium chloride complex equivalent in activity to 1 Gm. of streptomycin base.

**Streptomycin Calcium Chloride Complex:** 50 cc. vials containing streptomycin calcium chloride complex equivalent in activity to 5 Gm. of streptomycin base.

#### THE WM. S. MERRELL CO.

**Streptomycin Calcium Chloride Complex:** 1.3 Gm., 20 cc. vials. 1.3 Gm. of Streptomycin Calcium Chloride Complex equivalent to a 1.0 Gm. of Streptomycin base.

#### CHAS. PFIZER & Co., INC.

**Streptomycin Hydrochloride:** Bottles containing streptomycin hydrochloride equivalent in activity to 0.375 Gm. of streptomycin base.

**Streptomycin Sulfate:** Bulk.

**Streptomycin Sulfate:** Bottles containing streptomycin sulfate equivalent in activity to 1 Gm. of streptomycin base.

#### PREMO PHARMACEUTICAL LABORATORIES, INC.

**Streptomycin Hydrochloride:** Vials containing streptomycin hydrochloride equivalent in activity to 1 Gm. of streptomycin base (one million units).

E. R. SQUIBB & SONS

**Streptomycin Hydrochloride:** Streptomycin hydrochloride equivalent in activity to 1 Gm. of streptomycin base, 20 cc. vials and streptomycin hydrochloride equivalent in activity to 2 Gm. of streptomycin base, 40 cc. vials.

THE UPJOHN COMPANY

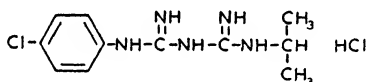
**Streptomycin Sulfate:** 30 cc. vials containing streptomycin sulfate equivalent in activity to 1 Gm. of streptomycin base (one million units).

**TYROTHRIN.**—(See under Local Anti-Infectives.)

## Antimalarial Agents

### Synthetic Compounds

**CHLORGUANIDE HYDROCHLORIDE.**— $N^1$ -(*p*-chlorophenyl)- $N^5$ -isopropylbiguanide hydrochloride.—The structural formula of chlorguanide hydrochloride may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Chlorguanide hydrochloride is useful for the prophylaxis, suppression and treatment of malignant tertian (*Plasmodium falciparum*) malaria and for the suppression and treatment of benign tertian (*Plasmodium vivax*) malaria with the strains so far studied. The drug is only partly effective in preventing attacks of vivax malaria since erythrocytic forms appear in the blood a short time after the drug is withdrawn. Other antimalarial drugs such as chloroquine or quinacrine are said to be preferred in the treatment of vivax malaria. Chlorguanide hydrochloride is the drug of choice for the treatment of falciparum malaria.

Chlorguanide hydrochloride disappears from the plasma in about 48 hours after the administration of a single dose of 0.5 Gm. About one-half to one-third of the drug is excreted by the kidneys. The drug does not accumulate in the body when given in therapeutic doses.

No toxic symptoms are observed in the usual dosage regimen, but doses of 1.0 Gm. or more may produce vomiting, abdominal pain, and diarrhea. Excessive doses may produce transient hematuria, epithelial cells, and casts in the urine. Intramuscular injection of chlorguanide hydrochloride may result in local myonecrosis and inflammatory reactions. High doses may also produce a temporary myelocytic reaction in the blood.



As with other antimalarial agents, the response of various strains of plasmodia to the drug is variable, so that the average dosage schedule indicated below may be subject to modification in accordance with the response of the strain involved.

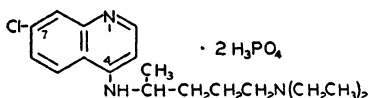
**Dosage.**—A single dose of 0.3 Gm. weekly in the suppression of falciparum and vivax malaria. For the prophylaxis of falciparum malaria, 0.1 Gm. twice weekly may be given; this dose is only partially effective against vivax malaria.

A dose of 0.1 Gm. three times daily, or 0.3 Gm. daily, for ten days is usually effective in producing a cure of falciparum malaria. The same dose is usually only partially effective against vivax malaria.

ABBOTT LABORATORIES

Tablets Chlorguanide Hydrochloride: 0.1 Gm. and 0.3 Gm.

**CHLOROQUINE DIPHOSPHATE.**—Aralen Diphosphate-Winthrop-Stearns.—7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline diphosphate.—The structural formula of chloroquine diphosphate may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Chloroquine diphosphate is highly active against the erythrocytic forms of *P. vivax* and *P. falciparum*. It does not prevent relapses in vivax malaria, nor will it prevent the establishment of vivax infection when administered as a prophylactic. It is, however, effective in vivax malaria as a suppressive agent and for the termination of acute attacks, significantly lengthening the interval between treatment and relapse.

In falciparum malaria, chloroquine diphosphate abolishes the acute attack and effects complete cure of the infection.

Chloroquine diphosphate has approximately three times the activity of quinacrine hydrochloride against standardized strains of *P. vivax* and *P. falciparum*.

Chloroquine diphosphate is rapidly and completely absorbed by the gastro-intestinal tract. Some of it is excreted slowly in the urine. Considerable amounts are deposited in the organs and tissues, and it is concentrated in nucleated cells, particularly those of the liver, spleen, kidneys and lung.

Chloroquine diphosphate is metabolised in the body, but this occurs slowly, and the drug may be detected in body tissues for more than a week after discontinuing medication. The drug is well tolerated in therapeutic doses and does not produce cinchonism nor discolor the skin. However, there may be mild headache, pruritis, visual disturbances, and gastro-intestinal com-

plaints following therapeutic doses. Blurring of vision and difficulty in focusing are occasionally observed following prolonged administration. None of the side reactions appear serious, and all have been of a reversible nature.

**Dosage.**—Chloroquine diphosphate is usually administered orally either before or after meals. For suppression of vivax malaria, a weekly dose of 0.5 Gm. given at exactly seven-day intervals is recommended.

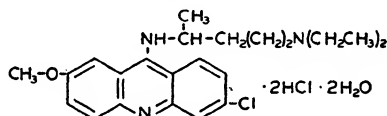
For treatment of acute attacks of vivax and falciparum malaria, an initial dose of 1.0 Gm. followed by an additional 0.5 Gm. after six to eight hours and a single dose of 0.5 Gm. on each of two consecutive days (total of 2.5 Gm. in three days) is sufficient to eradicate most infections with *P. falciparum* and to terminate an acute attack of vivax malaria. In the latter, freedom from clinical attacks may be maintained thereafter by administration of suppressive doses (0.5 Gm. weekly).

WINTHROP-STEARNs, INC.

**Tablets Aralen Diphosphate: 0.25 Gm.**

U. S. patent 2,233,970 (March 4, 1941; expires 1958). U. S. trademark registration pending.

**QUINACRINE HYDROCHLORIDE.**—U. S. P. —**Atabrine di-hydrochloride-Winthrop-Stearns.**—3-Chloro-7-methoxy-9-(1-methyl-4-diethylaminobutylamino)-acridine Dihydrochloride.—Mepacrine Hydrochloride.—“Contains not less than 77 per cent and not more than 80.2 per cent of quinacrine base,  $C_{23}H_{30}ClN_3O$ , corresponding to not less than 98 per cent of  $C_{23}H_{30}ClN_3O \cdot 2HCl \cdot 2H_2O$ .”—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Quinacrine Hydrochloride and Quinacrine Hydrochloride Tablets.

**Actions and Uses.**—Quinacrine hydrochloride destroys the asexual forms (trophozoites) of the causative organism in all types of malaria and thus checks the progress of the disease. Given during the first paroxysms of a benign tertian (*P. vivax*) attack it will often prevent completely the appearance of the third paroxysm while considerably lessening the severity of the second. At present the consensus is that in ordinary cases of benign type, and also in the more rare quartan (*P. malariae*) type, it gives better results than quinine. Some observers are of the opinion that relapses are less frequent than with quinine and that the period of treatment is shorter. Quinacrine hydrochloride is more effective than quinine in the treatment of malig-

nant subtertian (*P. falciparum*) malaria. It is of value in the treatment of blackwater fever when the treatment of quinine is contraindicated. Like quinine the drug effects partial destruction of the sexual forms (gametocytes) of the malarial organisms and thus lessens in some degree the extent to which the patient may act as a reservoir from which mosquitoes may be infected. If taken faithfully in suppressive dosage quinacrine hydrochloride will lengthen the interval between relapses of malaria, being in this regard perhaps somewhat more effective than quinine.

Quinacrine hydrochloride is reported to be effective in combating *Giardia lamblia* infestation, but the evidence that this organism is pathogenic for man or is the cause of diarrhea and other symptoms associated with its presence in the gastro-intestinal tract is inconclusive.

Quinacrine hydrochloride causes the urine to become very yellow on the third to fifth day, and, being of an acridine dye nature, it may cause temporary discoloration of the skin. Headache and relatively mild gastro-intestinal symptoms occur but not very frequently. The drug does not cause visual or aural disturbances and may therefore be preferred to quinine by patients who have experienced both drugs. The circulatory system does not seem to be disturbed by quinacrine hydrochloride in therapeutic dosage. The drug is not considered to be toxic to the liver or kidneys. Some patients claim to be stimulated by quinacrine hydrochloride. A relatively small number of psychotic attacks have been attributed to the drug—some quite severe—but no permanent derangements have been recorded. Apparently the drug may be used with safety in any stage of pregnancy though many observers withhold it in toxemia.

Quinacrine hydrochloride is absorbed readily from the intestine and is excreted slowly in the urine and feces. It is usually given by mouth but may also be given intravenously or intramuscularly, the latter route being preferred if injection must be resorted to at all.

#### *Dosage.*—

*Therapeutic Dose* for clinical malaria. Adults: 2 tablets of 0.1 Gm. each and sodium bicarbonate 1 Gm. by mouth with 200 to 300 cc. of water (or an equal amount of sweetened tea or fruit juice) every six hours for 5 doses, then 1 tablet of 0.1 Gm. 3 times daily for 6 days.

Children, 1 to 4 years: 1 tablet of 0.1 Gm. 3 times daily for the first day, then 1 tablet of 0.1 Gm. once daily for 6 days.

Children, 4 to 8 years: 2 tablets of 0.1 Gm. 3 times daily for the first day, then 1 tablet of 0.1 Gm. twice daily for 6 days.

Over 8 years: Same as adults.

*Suppressive Dose* in malarious areas. Adults: 1 tablet of 0.1 Gm. daily, preferably beginning two weeks in advance of exposure, and continuing for at least four weeks after last possible exposure in a malarious area.

Children: 1 tablet of 50 mg. daily.

*Suppressive Dose* in persons who have had attacks of vivax

malaria within 6 months, and no quinacrine (atabrine) for 3 weeks.

Adults: 1 tablet of 0.1 Gm. 3 times a day for 3 days, then 1 tablet of 0.1 Gm. daily.

Children: 1 tablet of 50 mg. 3 times a day for 3 days, then 1 tablet of 50 mg. daily.

*Note: Each dose, therapeutic or suppressive, should be taken with a full glass of water after a meal.*

The technic of the intramuscular or intravenous administration must be learned before the method is used. Details will be found in the circulars of manufacturers and in various publications.

WINTHROP-STEARNs, INC.

**Atabrine di-Hydrochloride Powder:** 0.2 Gm. ampuls, packaged with 10 cc. ampuls of sterile distilled water.

**Tablets Atabrine di-Hydrochloride:** 50 mg. and 0.1 Gm. (plain) and 0.1 Gm. (sugar coated).

U. S. patent 2,113,357 (April 5, 1938; expires 1955). U. S. trademark 302,473.

### *Naturally Occurring Compounds*

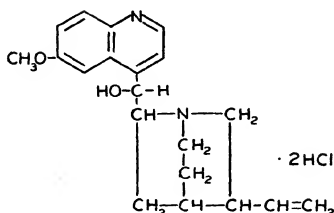
The action of quinine is essentially the same in all its compounds. Where oral medication is not feasible quinine derivatives may be administered by intravenous injection, but this should be reserved for emergency cases of severe malarial infection and with due cognizance that this route of administration may produce a marked fall in blood pressure. For such use, solutions of quinine salts should be diluted to a concentration not greater than 0.5 per cent and should be injected very slowly. The subcutaneous or intramuscular routes should not be employed because of the danger of local tissue damage. In those rare cases where neither oral nor intravenous administration is possible, the use of other antimalarial drugs should be resorted to.

Some of the esters also contain other therapeutically active radicals (phenetidin, salicyl, etc.). When liberated these produce their characteristic effects; but it is doubtful whether the combinations of several therapeutically active radicals in fixed proportions are superior to simple mixtures of the ingredients.

Totaquine, U. S. P., which is a mixture of alkaloids from the bark of species of *Cinchona* containing not less than 70 per cent of the total crystallizable alkaloids has been developed for use in the treatment of malaria in the same manner as quinine compounds.

**QUININE DIHYDROCHLORIDE-U. S. P.**—"The dihydrochloride of an alkaloid obtained from cinchona." U. S. P.

For description and standards see the U. S. Pharmacopeia under Quinine Dihydrochloride and The National Formulary under Quinine Hydrochloride Ampuls. The structural formula may be represented as follows:



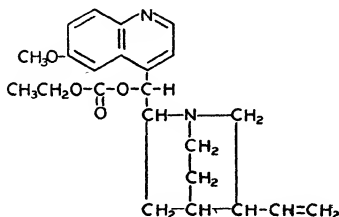
**Actions and Uses.**—Quinine Dihydrochloride has actions similar to those of quinine, over which it has the advantage of being more soluble in water. It is used where aqueous solutions of quinine are desired for intravenous injection in those cases of severe malarial infection where oral medication is not feasible. It should not be administered by subcutaneous or intramuscular injection because of the danger of local tissue damage. The absorption of intramuscular injections of quinine salts is slower than that following oral administration. Solutions of quinine dihydrochloride for intravenous administration should be diluted to a concentration not greater than 0.5 per cent and should be given slowly and with due cognizance of the danger of a serious fall in blood pressure, particularly in patients with cardiovascular impairment.

**Dosage.**—From 0.24 to 0.65 Gm., suitably diluted, is given intravenously as indicated by the severity of the symptoms and the age of the patient. The dose of 0.65 Gm. should not be repeated more than three times in twenty-four hours. Oral administration should be resumed as early as possible.

ENDO PRODUCTS, INC.

**Solution Quinine Dihydrochloride:** 0.25 Gm. in 1 cc.; 0.5 Gm. in 1 cc.; 1.0 Gm. in 2 cc. ampuls. Each ampul contains the stated amount of quinine dihydrochloride dissolved in distilled water.

**QUININE ETHYLCARBONATE-N. F. — Euquinine-Merck.**—"The ethylcarbonate of an alkaloid usually obtained from cinchona." *N. F.* The structural formula may be represented as follows:



For description and standards see The National Formulary under Quinine Ethylcarbonate.

*Actions and Uses.*—Quinine ethylcarbonate is used in place of quinine sulfate and similar soluble quinine salts when a practically tasteless quinine compound is preferred.

*Dosage.*—1 Gm.

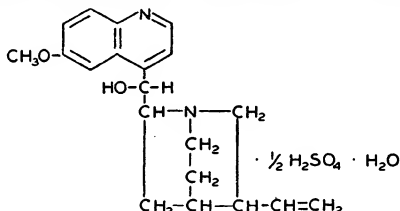
MALLINCKRODT CHEMICAL WORKS

**Quinine Ethyl Carbonate (Powder):** bulk.

MERCK & Co., INC.

**Euquinine (Quinine Ethylcarbonate Crystals):** bulk.

**QUININE SULFATE-U. S. P.—Coco-Quinine-Lilly.**—  
“The sulfate of an alkaloid obtained from cinchona.” U. S. P.  
The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Quinine Sulfate and The National Formulary under Quinine Sulfate Capsules.

*Actions and Uses.*—Quinine is a protoplasm poison, affecting protozoa more than bacteria. It is somewhat irritating to the stomach and intestines and when absorbed it may cause ringing in the ears, but moderate doses usually produce no other marked effects in healthy persons though hypersensitiveness to quinine is not rare. In patients with fever it is antipyretic. It is used chiefly as a specific in malaria. In this disease it should be given in large doses several hours before the time of the expected chill. Toxic doses produce depression of the heart and respiration, and collapse. Such doses may produce more or less complete amblyopia terminating in permanent loss of sight. Moderately large doses of quinine act as a stimulant to the uterine muscles, but do not produce such spasmodic contractions as ergot. Quinine may be used as a tonic, as are the simple bitters, for the improvement of digestion and nutrition. It has recently come into use for the treatment of myotonia, for which large doses may be required. Its solutions, and especially those of quinine and urea hydrochloride, produce local anesthesia. The ordinary quinine salts are irritant.

*Dosage.*—1 Gm. daily. For ordinary use it is preferably administered in the form of capsules. For use as a bitter tonic 0.1 Gm. is given in solution.

## ELI LILLY AND COMPANY

**Syrup Coco-Quinine:** Each 100 cc. contains quinine sulfate, 2.19 Gm. suspended in a syrup flavored with chocolate, yerba santa and vanillin, and containing sodium benzoate 0.18 Gm. per 100 cc., and alcohol per cent.

U. S. trademark 174,144.

## Antiprotozoan Agents

## Antimony Compounds

**ANTIMONY THIOGLYCOLLAMIDE.**—The triamide of antimony thioglycollic acid,  $\text{Sb}(\text{S} \cdot \text{CH}_2\text{CO} \cdot \text{NH}_2)_3$ . It contains not less than 30 per cent of antimony.

For tests and standards, see Section B.

**Actions and Uses.**—Antimony thioglycollamide and antimony sodium thioglycollate are used in the treatment of schistosomiasis, leishmaniasis (kala azar), and are proposed for use in the treatment of granuloma inguinale. These substances have been found to be less toxic and less irritating than antimony and potassium tartrate. The thioglycollamide has proved to be somewhat more toxic than the thioglycollate. The former is also less soluble but it has the advantage of being more stable. The drugs are used intramuscularly or intravenously.

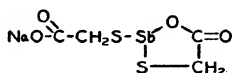
**Dosage.**—The usual intramuscular or intravenous dose employed by Randall is 0.08 Gm., dissolved in 20 cc. of sterile water every second day until from 15 to 25 injections have been given. He recommends that at least 12 injections be given after the first healing has taken place to insure permanent cure. Solutions of antimony thioglycollamide are incompatible with solutions of the fixed alkalis.

HYNSON, WESTCOTT & DUNNING, INC.

**Antimony Thioglycollamide (Powder):** bulk.

**Solution Antimony Thioglycollamide, 0.4%:** 10 cc. ampuls.

**ANTIMONY SODIUM THIOGLYCOLLATE.**—U. S. P.—“When dried at 100 C. for 4 hours, contains not less than 35.5 and not more than 38.5 per cent of Sb [antimony], corresponding to not less than 94.7 per cent  $\text{C}_4\text{H}_4\text{O}_4\text{NaS}_2\text{Sb}$ .” U. S. P.—Antimony sodium thioglycollate is formed by dissolving antimony trioxide in a solution of a mixture of sodium thioglycollate and thioglycollic acid. The structural formula may be represented as follows:



For description and standards see The U. S. Pharmacopeia

under Antimony Sodium Thioglycollate and Antimony Sodium Thioglycollate Injection.

**Actions and Uses.**—The same as for antimony thioglycollamide. It is more soluble than antimony thioglycollamide, and in higher dosages it appears to be less toxic.

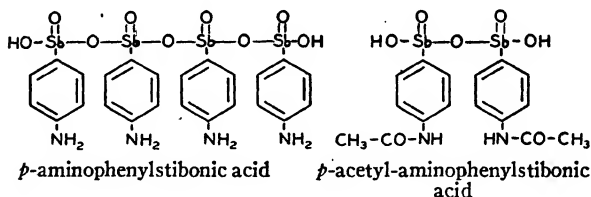
**Dosage.**—From 0.05 to 0.1 Gm. dissolved in 10 to 20 cc. of sterile water every third or fourth day until from 15 to 25 injections have been given. Its solutions are incompatible with solutions of the fixed alkalis.

HYNSON, WESTCOTT & DUNNING, INC.

**Antimony Sodium Thioglycollate (Powder):** bulk.

**Solution Antimony Sodium Thioglycollate 0.5%:** 10 cc. ampuls.

**ETHYLSTIBAMINE.** — **Neostibosan - Winthrop - Stearns.**—A pentavalent antimony-organic complex mixture consisting of *p*-aminophenylstibonic acid, largely as a tetramer; *p*-acetylaminophenylstibonic acid, largely as a dimer; antimononic acid, and diethylamine in the approximate molar ratio of 1:2:1:3, respectively. The structural formulas of the *p*-aminophenylstibonic acid tetramer and the *p*-acetylaminophenylstibonic acid dimer may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The pharmacologic effects of antimony preparations depend to some extent on the rapidity with which like antimony is freed from the complex compound. Like all organic antimony compounds, Neostibosan, particularly if injected rapidly into the circulation, may produce a transient fall in systemic blood pressure, due partly to a diminished output of the left ventricle and partly to dilatation of the splanchnic vessels. At the same time, there is a rise in pulmonary blood pressure. Large doses have a depressing effect upon respiration.

After intravenous administration of an average adult dose, it has been found that 41 per cent of the drug is found in the urine during the first twenty-four hours, 6 per cent during the subsequent twenty-four hours, and approximately 1 per cent during the third twenty-four hour period. Following intra-



muscular administration of the same dose, the figures were 34 per cent, 3 per cent and 1.5 per cent, respectively. The remainder is excreted slowly. Immediate distribution of antimony following a single injection of Neostibosan seems to be dependent on physical factors; no one organ appears to possess immediate affinity. However, following a series of injections, considerable quantities of antimony, which is excreted through the kidneys, may be found in the kidneys and liver.

Included in the reactions that may be encountered are fever, cough, vomiting, nausea, headache, lymphadenitis, skin eruptions, diarrhea, pain in the abdomen, convulsions, nephritis, jaundice, bronchopneumonia and necrosis of the gums. The drug is contraindicated in the presence of nephritis, pulmonary tuberculosis, pneumonia, heart disease, jaundice, diarrhea and ascites.

Ethylstibamine is used in the treatment of certain forms of leishmaniasis (kala-azar, dermal leishmaniasis) but the exact manner by which antimony compounds bring about a cure is unknown; it does not seem to be the result of a direct action on the parasites. Like other pentavalent organic antimony preparations, it is considered less toxic and more effective against kala-azar than trivalent organic antimony compounds.

**Dosage.**—From 8 to 10 injections are administered daily or every other day. It may be injected intravenously or intramuscularly. A 5 per cent solution is usually employed for intravenous use and a 25 per cent solution (isotonic) for intramuscular injection. *It must be administered slowly.* Solutions should be used immediately and must not be heated. Diet during treatment should be light and easily digestible; the patient should rest for several hours after each injection.

The initial dose for infants is 0.05 Gm.; subsequent doses are increased to 0.1 Gm. For children 2 to 4 years, the initial dose is 0.05 to 0.1 Gm., subsequent doses increased to 0.2 Gm.; 5 to 9 years, initial dose is 0.1 Gm. to 0.2 Gm., subsequent doses increased to 0.25 Gm.; 10 to 15 years, 0.2 Gm. for the initial dose, subsequent doses being increased to 0.3 Gm. Adults may receive 0.2 Gm. as the initial dose, and up to 0.3 Gm. for subsequent doses.

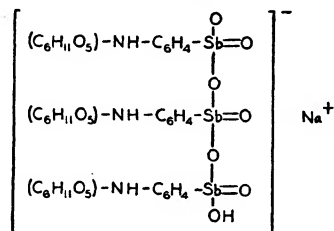
WINTHROP-STEARNs, INC.

**Neostibosan:** 0.3 Gm. ampuls.

U. S. patent 1,988,632. U. S. trademark 400,894.

**STIBAMINE GLUCOSIDE.**—A nitrogen glucoside of sodium *p*-aminophenylstibonate.—A product of incompletely defined structure prepared by the condensation of *p*-aminophenylstibonic acid and glucose in a slightly basic solution, followed by precipitation with absolute alcohol and final drying. The rational formula provisionally assigned to stibamine gluco-

side is based upon the assumption of a trimer linked through the stibonic group,  $C_{38}H_{49}O_{22}N_3Sb_3Na$ . Stibamine glucoside may be represented by the following structural formula:



For tests and standards, see Section B.

*Actions and Uses.*—Stibamine glucoside shares the antiprotozoan action of other pentavalent organic antimony compounds. In general, these are somewhat less toxic than trivalent organic antimony compounds and are considered more effective in the treatment of most forms of leishmaniasis (kala-azar) but are of little value in South American leishmaniasis (muco-cutaneous) and against the helminths of schistosomiasis (bilharziasis) and filariasis. Trivalent antimony is also usually preferred for the treatment of granuloma inguinale. Antimony compounds have been largely replaced by pentavalent organic arsenicals for the treatment of trypanosomiasis.

Stibamine glucoside, in common with other pentavalent organic antimony compounds, produces fewer side reactions than trivalent organic antimony and may be injected intramuscularly. Reactions include vomiting (about 20 minutes after injection), and occasionally diarrhea. Anaphylactoid reaction, characterized by an urticarial eruption, husky voice and, in severe cases, collapse may be encountered after the sixth or seventh injection. Hepatitis is a rare but serious reaction that calls for immediate cessation of medication.

It is contraindicated in the presence of pneumonia, nephritis, jaundice or ascites.

*Dosage.*—Stibamine glucoside administered intravenously, but may be given intramuscularly when superficial veins are not accessible. The suggested average dose is calculated on the basis of 0.1 Gm. per 100 lb. (45.4 Kg.) of body weight, administered as a freshly prepared 4 per cent solution (0.1 Gm. in 2.5 cc. of sterile distilled water). It is rarely necessary to exceed a maximum single dose of 0.2 Gm. Injections are usually given on alternate days for a course of treatment not to exceed a total dosage of 3 Gm. per 100 lbs. of body weight. This is usually considered sufficient to eradicate infection. A more rapidly effective method of treatment consists in giving daily injections, commencing with an initial dose of 0.05 Gm. per 100 lb. of body

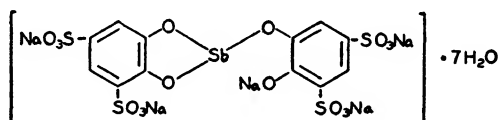
weight that is increased daily by 0.05 Gm. to 0.3 Gm. per 100 lb. body weight and then held at that amount daily until a total dosage, not to exceed 2.55 Gm. per 100 lb. body weight, has been given. This more intensive course requires strict observation for the appearance of toxic symptoms. In antimony-susceptible individuals or in whom anaphylactoid reaction is considered likely because of a previous course of treatment, it is considered advisable to employ an initial dose of 0.05 Gm. per 100 lbs. of body weight, and to increase subsequent doses gradually as and when tolerance is established.

Only solutions prepared from freshly opened containers should be used. The solution should not be warmed for injection and should not be used after more than one hour has elapsed since its preparation.

BURROUGHS WELLCOME & Co.

**Neostam Stibamine Glucoside:** 0.1, 0.2 and 0.5 Gm. vials. Each vial contains the stated quantity of stibamine glucoside hermetically sealed under nitrogen to preserve stability.

**STIBOPHEN-N. F. — Fuadin-Winthrop-Stearns.** — Sodium antimony III bis-catechol-2,4 disulfonate.—It contains 13.6 per cent of trivalent antimony. "Stibophen contains not less than 15.6 per cent and not more than 16.0 per cent of trivalent Sb, calculated on a moisture-free basis, the moisture being determined on a separate portion." *N. F.* The structural formula may be represented as follows:



For description and standards see The National Formulary under Stibophen and Stibophen Ampuls.

**Actions and Uses.**—Stibophen is proposed for use in the treatment of granuloma inguinale and of schistosomiasis (bilharziasis): Its action is reported to be more rapid and efficient in early granuloma inguinale than in the later stages when there is scar formation. It is necessary to keep the treatment up for some time after all evidence of the disease has disappeared. In schistosomiasis it is indicated together with iron as the treatment of choice in the intestinal stage of the disease. The iron salts should be given after the completion of the treatment and not concurrently. The anemia, when present, is apparently due to a prolonged iron deficiency.

**Dosage.**—Intramuscularly (rarely intravenously), first day 1.5 cc., second day 3.5 cc., and on the third, fifth, seventh, ninth, eleventh, thirteenth and fifteenth days 5 cc., a total of 40 cc. of the 6.3 per cent solution. Following healing in a week or two weeks the course may be repeated and thereafter the drug is

given once a week and then every fourteen days for several weeks to prevent relapse.

WINTHROP-STEARNs, INC.

**Solution Fuadin:** 3.5 cc. and 5 cc. ampuls. Each 1 cc. contains Fuadin, 63 mg.; sodium bisulfite, not more than 0.125 per cent.

U. S. patents 1,549,154 (Aug. 11, 1925; expired) and 1,873,668 (Aug. 23, 1932; expires 1949). U. S. Trademark 304,950.

### *Arsenic Compounds*

In some of the compounds listed in this chapter, the arsenic is pentavalent; in others it is trivalent. A typical arsenic reaction results only from the trivalent arsenic, and in order to secure this action from those compounds containing pentavalent arsenic, their arsenic must be reduced to the trivalent form; this is done by the body, but the rate at which the reduction occurs varies greatly with the different compounds. In some cases, the desirable, as well as the undesirable, effects produced by these compounds are due to the arsenic which is slowly rendered active; in others the therapeutic effects may be due, at least in part, to the unaltered molecules. The diseases in which arsenic therapy has proved useful are particularly those caused by protozoa. Inorganic arsenic will kill protozoa, but it cannot be administered so as to reach the protozoa in fatal quantity. In the body, the organic compounds are less toxic to mammals and more toxic to protozoan parasites.

Among the advantages claimed for, or known to be possessed by, these compounds, the following may be mentioned: In those known to produce their effects through the liberation of arsenic, the arsenic is liberated slowly; some remain in the circulating blood for a much longer period than do inorganic arsenic compounds and thus remain longer in contact with parasites which it is desired to kill; some are specifically etiotropic, that is, they have a much greater affinity for the parasites causing the disease than they have for the tissues of the host.

Preparations of arsenic used intravenously come under the federal law covering serums, viruses, toxins and analogous products, and are subject to the same control.

### **Compounds Containing Trivalent Arsenic**

According to Ehrlich's view, only trivalent arsenic is markedly toxic to spirochetes, trypanosomes, etc.; hence he introduced a number of such compounds. Of these only the compounds in which the toxicity is reduced or modified by the introduction into the molecules of certain groups are listed below. These compounds have, according to Ehrlich, a special affinity for certain organisms, particularly spirochetes, while their toxicity for the higher animals is comparatively low. The exact fields of usefulness of these compounds and their limitations, and also the best methods of administering them, are still under discussion.

The toxic actions of arsphenamine are ascribed to the arsenic component in some cases. In other cases the decomposition of the solution has been assigned as a cause. Undoubtedly some reactions are due to idiosyncrasies on the part of the patient. However, there is seen a large group of these cases which must be explained otherwise. Certainly, improper technique in the preparation of the drug, as well as the improper (for example, too rapid) administration of the arsphenamines may add to the inherent toxicity. The administrator should always carefully observe the directions supplied by the manufacturers. If this be done and there are still reactions, then only should one look elsewhere for the causation.

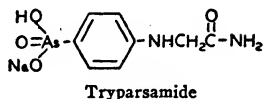
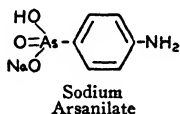
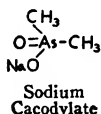
The water used should be, if possible, freshly distilled and freshly sterilized. All chemicals should be pure. Any rubber tubing employed for the first time should be soaked over night in 5 per cent sodium hydroxide solution, then boiled in distilled water and thoroughly washed with the same. Some reactions are undoubtedly due to administration of the drug to a patient on a full stomach or to one not properly prepared by previous catharsis. It is always well to start the use of arsenicals with a small dose—because of possible idiosyncrasies.

One should not be too much alarmed in a fresh case of syphilis by the reaction seen after the first injection of the arsphenamines—the Herxheimer reaction. It is that phenomenon of the reaction of the disease to the arsphenamine in which there is a rise of temperature, headache, possible nausea, malaise, and marked accentuation of the cutaneous and mucous membrane symptoms. One should be concerned, however, if with succeeding injections there are promptly recurring reactions in the form of gastritis, itching of the skin, urticaria, conjunctivitis, fixed areas of dermatitis that flare up with each new injection, and more or less generalized dermatitis or jaundice. In addition, there are sometimes noted generalized exfoliative dermatitis, purpura hemorrhagica, aplastic anemias, acute yellow atrophy and encephalitis.

The best treatment of these conditions is prophylaxis, and these drugs should never be readministered without inquiry of the patient and examination of the skin as to possible pruritus, jaundice, cutaneous eruptions, or other symptoms. Moreover, a urine examination should always be a preliminary. 2,3-Dimercaptopropanol (BAL) has been used in the treatment of hemorrhagic encephalitis and dermatitis due to arsenotherapy. Further discussion of this technic may be found in the Chapter on Unclassified Therapeutic Aids.

Arsphenamines are contraindicated or should be used with special caution in diseases of the eye of a nonsyphilitic character, in severe affections of the heart and blood vessels, the lungs and the kidneys and in advanced degenerative processes in the central nervous system. They should also be used with caution in infants. Arsphenamine should not be used in beginning luetic optic

neuritis until after some preliminary antiluetic therapy with either bismuth or mercury salts.



Arsanilic acid is derived from arsenic acid,  $\text{AsO}(\text{OH})_3$  by replacing one hydroxyl by aniline (phenylamine)  $\text{C}_6\text{H}_5\text{NH}_2$ ; related compounds are made by substituting derivatives of aniline.

The compounds containing pentavalent arsenic are comparatively nontoxic when introduced into the animal system until changes take place that liberate the arsenic. When they are slowly decomposed, they produce favorable effects. If the reduction takes place with greater rapidity, they may produce ordinary arsenic poisoning.

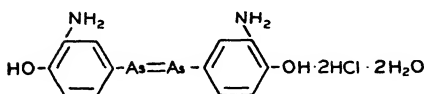
Sodium cacodylate is excreted partly unchanged and partly as cacodylic oxide, which gives a foul odor to the breath, perspiration, etc. Further changes yield products containing inorganic, trivalent arsenic, by which the therapeutic effects, if there are any, are produced. It is not used in the treatment of syphilis.

Sodium arsanilate acts with especial violence on the optic nerve, producing optic atrophy, frequently resulting in permanent blindness. This may occur unfortunately even with therapeutic doses. It is not used in the treatment of syphilis.

Tryparsamide is a powerful trypanocide and only slightly trepanemacidal. The drug, according to studies of Voegtlin and co-workers, when injected intravenously results in pronounced penetration of the nervous system tissue. This may explain its value in the treatment of resistant syphilis of the central nervous system. It may be used following malaria therapy. The suggestion has been made by Young and Loevenhart that the effect on the optic nerve frequently seen after tryparsamide is due to the presence of the amino group in the para position to the arsenic (Stokes). Because of this fact the physician should exercise great caution in the use of this drug.

### Compounds Containing Trivalent Arsenic

**ARSPHENAMINE-U. S. P.**—3,3-Diamino-4,4-dihydroxy-arsenobenzene Diaminodihydrovyarsenobenzene Dihydrochloride. —“Contains not less than 30 per cent and not more than 32 per cent of arsenic (As).” *U. S. P.* It complies with the requirements of the National Institute of Health, United States Public Health Service. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Arsphenamine.

*Actions and Uses.*—Arsphenamine is useful as a specific remedy for syphilis in all stages. According to available data, in incipient tabes, early paresis and cerebrospinal syphilis the drug can be employed with the prospect of most benefit in those cases in which its use is begun early.

The drug is used in the spirillum affections, such as relapsing fever and frambesia.

The remedy is contraindicated in severe disturbances of the circulatory organs, advanced degenerations of the central nervous system and cachexias, unless these are a direct result of syphilis; it is also contraindicated in patients who have pronounced idiosyncrasy against arsenic.

It has been employed successfully in various types of syphilitic diseases of the eyes. As a rule in such cases it is well to give a preliminary course of mercury or bismuth injections in order to obviate the danger of a Herxheimer reaction. Repeated injections should be given. It may be used up to 0.01 Gm. per kilogram of body weight, but it is better to keep under this dose.

*Dosage.*—Usually from 0.2 to 0.4 Gm.; though 0.6 Gm. may be given, the smaller doses are more extensively used.

For children from 0.1 to 0.2 Gm. In infants doses of from 0.02 to 0.1 Gm. may be used. The dose should be varied according to the strength and condition of the patient. The intravenous method is preferable and is to be recommended.

For intravenous injection one should proceed thus:

The ampul containing the drug is immersed in alcohol, in order to be sure that a cracked tube is not being used; then the tube is carefully wiped off, the neck filed across and broken off, and the contents sprinkled on sterile distilled water (10 cc. for each 0.1 gram of the drug used), contained in a sterile Erlenmeyer flask. The drug is allowed to dissolve with little or no agitation. Normal sodium hydroxide is then added to the solution, using 0.85 cc. to every 0.1 Gm. of the drug. Thus 0.6 Gm. of the drug would require 5.1 cc. of normal alkali. A precipitate of the base is first formed, which, after the contents are carefully agitated, is again brought into solution, the fluid being strongly alkaline. Filter the alkalized solution through sterile gauze, 4 ply, and dilute the filtrate with sterile distilled water to make 25 cc. for each 0.1 Gm. of the drug. It should stand 30 minutes before using. At least one minute should be allowed for each 25 cc. of the solution to flow into the vein, using the gravity method. The directions accompanying the drug as to temperature of the water, etc., should be followed. The contents of a tube should be mixed at once after opening, and under no circum-

stances should the contents of a tube damaged in transportation or any remnants of the powder from previously opened tubes be used. In all cases the skin should be disinfected with tincture of iodine or with alcohol.

MERCK & Co., INC.

**Arsphenamine:** 0.1 Gm., 0.2 Gm., 0.3 Gm., 0.4 Gm., 0.5 Gm., 0.6 Gm., 1.0 Gm. and 3.0 Gm. ampuls.

**BISMUTH ARSPHENAMINE SULFONATE—Bismarsen-Abbott.**—Sulfarsphenamine Bismuth.—Bismuth Arsphenamine Sulfonate.—The sodium salt of a bismuth derivative of arsphenamine methylene sulfonic acid (the exact structural formula of which has not been established) with inorganic salts. It contains approximately 13 per cent of arsenic and 24 per cent of bismuth.

Bismuth arsphenamine sulfonate is prepared by adding a solution of potassium bismuth tartrate in water to an aqueous solution of 3,3'-diamino-4,4'-dihydroxy-arsenobenzene-N,N'-dimethylene sulfonate, dissolving the precipitate with a measured quantity of sodium hydroxide solution, precipitating by pouring the clear solution into a methyl alcohol-ether mixture and filtering off the precipitate and drying it in vacuo.

For tests and standards, see Section B.

**Actions and Uses.**—For the treatment of syphilis. The drug is said to be somewhat slower in its action than intramuscularly administered sulfarsphenamine or intravenously administered neoarsphenamine. Some pain at the site of injection may be noted.

**Dosage.**—Bismuth arsphenamine sulfonate is administered intramuscularly. The initial dose is 0.1 Gm.; succeeding doses are 0.2 Gm. A 0.1 Gm. dose is dissolved, at the same time of administration, in 1 to 2 cc. of a sterile aqueous solution of 0.25 per cent butyn sulfate. Weekly doses may be later increased to biweekly doses in courses of treatment of twenty doses, or more.

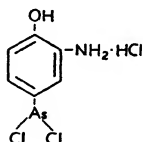
ABBOTT LABORATORIES

**Bismarsen:** 0.1 Gm. and 0.2 Gm. ampuls; accompanied, respectively, by 1 cc. and 1¾ cc. ampuls of a sterile, aqueous solution of 0.25 per cent butyn sulfate.

U. S. patent 1,605,691 (Nov. 2, 1926; expired). U. S. trademark 230,625.

**DICHLOROPHENARSINE HYDROCHLORIDE—U. S. P.—Clorarsen-Squibb.**—2-Amino-4 hydroxyphenyl Dichloroarsine.—“Dichlorophenarsine Hydrochloride, when dried in a vacuum desiccator over phosphorus pentoxide for twenty-four hours, contains not less than 25.3 per cent and not more than 27 per cent of total arsenic (As).”—U. S. P. The structural formula may be represented as follows:





For description and standards see the U. S. Pharmacopeia under Dichlorophenarsine Hydrochloride.

**Actions and Uses.**—In recent literature may be found reports of an arsenical antisyphilitic agent which apparently was discovered in the early part of this century but was cast aside as being too toxic for clinical use. Some years later there were published reports on its use in animals and in the treatment of yaws and human syphilis. It was not until 1941 that 3-amino-4-hydroxyphenyl dichloro-arsine hydrochloride was found satisfactory for the treatment of syphilis; apparently the earlier studies were based on the use of an unbuffered compound which would provide a very low *pH*.

The preparations now available on the market contain sufficient alkaline buffering agent to make neutral a prepared solution for injection. They contain approximately 26 per cent of trivalent arsenic. On the addition of sterile distilled water to an ampul containing the mixture of dry dichlorophenarsine hydrochloride and alkaline buffer a reaction takes place, with the result that arsenoxide is supposed to be formed. It has been claimed that the latter agent is the therapeutically active part of the compound.

(A preliminary report of the Council appeared in *THE JOURNAL*, Sept. 25, 1943, p. 208.)

**Dosage.**—Initial dose for adults 45 mg. (0.045 Gm.) intravenously. The second dose may be increased up to 68 mg. (0.068 Gm.). The maximum dose may be regarded as 68 mg. (0.068 Gm.). Injections may be given every four to five days, since the drug is excreted rapidly.

For children, the initial dose should not exceed 0.5 mg. per kilogram of body weight; the later doses should average between 0.5 mg. and 1.0 mg. per kilogram of body weight.

#### ABBOTT LABORATORIES

**Dichlorophenarsine Hydrochloride:** Ampuls 45 mg., 68 mg. and multiple dose ampuls of 0.45 Gm. and 0.68 Gm.

#### E. R. SQUIBB & SONS

**Clorarsen:** 45 mg. and 67 mg. ampuls and multiple dose ampuls of 0.45 Gm. and 0.67 Gm. Each ampul contains the stated quantity of dichlorophenarsin hydrochloride admixed with three and one-third times its weight of a mixture containing sodium citrate 96 parts and sodium carbonate 4 parts.

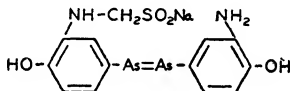
U. S. trademark 395,170.

WINTHROP-STEARNs, INC.

**Dichlorophenarsine Hydrochloride:** Ampuls 45 mg. and multiple dose ampuls 0.45 Gm. Each ampul contains, in addition to each 45 mg. of dichlorophenarsine hydrochloride, 25 mg. of anhydrous sodium carbonate, 45 mg. of sodium chloride and 80 mg. of sucrose.

**Dichlorophenarsine Hydrochloride:** Ampuls 68 mg. and multiple dose ampuls of 0.68 Gm. Each ampul contains, in addition to each 68 mg. of dichlorophenarsine hydrochloride, 37 mg. of anhydrous sodium carbonate, 28 mg. of sodium chloride and 0.102 Gm. of sucrose.

**NEOARSPHENAMINE-U. S. P.—Neosalvarsan-Winthrop-Stearns.**—"Consists chiefly of sodium 3,3'-diamino-4,4'-dihydroxyarsenobenzene-N-methanol sulfoxylate. It contains not less than 19 per cent of arsenic (As)." *U. S. P.* It complies with the requirements of the National Institute of Health, United States Public Health Service. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Neoarsphenamine.

**Actions and Uses.**—Neoarsphenamine is a modified soluble compound of arsphenamine; its action and uses are those of arsphenamine. Neoarsphenamine and Metaphen have been proposed for the treatment of Vincent's Angina and stomatitis.

**Dosage.**—Neoarsphenamine is probably less toxic than arsphenamine and, since it contains less arsenic, it is given in larger doses than arsphenamine. The average dose for a man is 0.45 to 0.60 Gm., with 0.45 Gm. as the minimum and possibly 0.75 Gm. as the maximum only for very large men. For women, 0.45 Gm. is the average if the patient is about the normal in weight; 0.3 Gm. would be the minimum and 0.6 Gm. the maximum, the latter dose being given only to large women. Children may be given 0.1 to 0.2 Gm. The limit dose is 15 mg. per kilogram of body weight. Here again a smaller dose is preferable.

Neoarsphenamine may be administered by intravenous or intramuscular injection, the former being considered decidedly preferable; the drug must not be administered subcutaneously. For intravenous gravity injection, 12.5 cc. of freshly distilled water should be used for each 0.1 Gm. of neoarsphenamine.

Neoarsphenamine may be employed intravenously in concentrated solutions. For this purpose as much as 0.1 Gm. may be dissolved in 0.5 cc. of sterile freshly distilled water; the injection is made with a syringe instead of by gravity. It is well

to draw out an equal amount of blood into the syringe containing the neoarsphenamine solution before reinjecting into the blood stream. It should be injected very slowly.

The ampul containing the drug is immersed in alcohol to detect a possible crack, then carefully wiped off; the neck filed across and broken off, and the contents sprinkled on the surface of cool, sterile distilled water and allowed to dissolve *without shaking* the solution. Any product incompletely soluble should be discarded. Solutions of neoarsphenamine must be injected *immediately* after their preparation. Neoarsphenamine must not be warmed and the temperature of the injected fluid should not be more than 20 to 22 C. (68 to 71.6 F.).

Neoarsphenamine may undergo deterioration in the ampule, and care should be exercised to use a drug of normal color and free solubility. The drug in fresh solution should be of canary yellow color. This drug should preferably be kept in a cool dark room or ice box and be not more than 6 months old.

Neoarsphenamine 0.04 Gm. is dissolved with 4 cc. of the 1:1,000 aqueous solution of Metaphen and the resultant solution is applied topically.

*Caution—Solutions of Neoarsphenamine must be freshly prepared when required for use. The solution should not be shaken during its preparation.—U. S. P.*

#### ABBOTT LABORATORIES

**Neoarsphenamine:** 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., and 4.5 Gm. ampuls.

**Neoarsphenamine and Metaphen:** Packages containing five ampules of neoarsphenamine, 40 mg. each, and one bottle of metaphen solution 1:1,000 (20 cc.).

#### MERCK & Co., INC.

**Neoarsphenamine:** 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 3.0 Gm. and 4.5 Gm. ampuls.

#### E. R. SQUIBB & SONS

**Neoarsphenamine:** 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 3.0 Gm. and 4.5 Gm. ampuls.

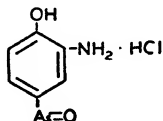
#### WINTHROP-STEARNs, INC.

**Neosalvarsan:** 0.15 Gm., 0.3 Gm., 0.45 Gm., 0.6 Gm., 0.75 Gm., 0.9 Gm., 1.5 Gm., 1.8 Gm., 3.0 Gm. and 4.5 Gm. ampuls.

U. S. trademark 88,862; 187,455.

**OXOPHENARSINE HYDROCHLORIDE—U. S. P.—**  
**Mapharsen—Parke, Davis.**—3-Amino-4-hydroxyphenyl Ar-sineoxide Hydrochloride. "Oxophenarsine Hydrochloride, when dried in a vacuum desiccator over phosphorus pentoxide for 24 hours, contains not less than 30 per cent and not more than 32 per

cent of total arsenic (As)." *U. S. P.* It complies with the requirements of the National Institute of Health, United States Public Health Service and must be released by the Institute. The structural formula may be represented as follows:



For description and standards see The U. S. Pharmacopeia under Oxophenarsine Hydrochloride.

**Actions and Uses.**—Oxophenarsine hydrochloride is proposed for the treatment of syphilis. It is stated to exhibit a relatively constant parasitocidal value. It is claimed to have a rapidly beneficial effect, particularly on early syphilis, causing the disappearance of spirochetes, healing of lesions and reversal of positive Wassermann reactions in a large percentage of cases. The reactions following the use of oxophenarsine hydrochloride are less severe than those observed after the use of the arsphenamines.

**Dosage.**—Intravenously, 0.03 Gm. for women and 0.04 Gm. for men, initially. The dose may be increased at the second injection to 0.04 Gm. for women and 0.06 Gm. for men. The maximum dose which should not be given any patient at the first injection, may be regarded as 0.06 Gm. Injections may be given every four or five days, since it is excreted very rapidly from the kidney. For children, the initial dose should not exceed 0.0005 Gm. (0.5 mg.) per kilogram of body weight; the total dose should average between 0.0005 and 0.001 Gm. (between 0.5 and 1 mg.) per kilogram of body weight.

It should be noted that the dosage of oxophenarsine hydrochloride is much lower than that of the arsphenamines.

PARKE, DAVIS & COMPANY

**Mapharsen:** 40 mg. and 60 mg. ampuls.

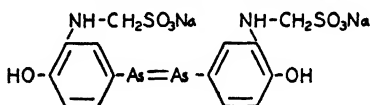
**Mapharsen:** 0.6 Gm. (multiple dose) ampuls. *Caution: These ampuls are hospital packages and represent either 10 doses at 60 mg. or 15 doses at 40 mg.*

Each of the ampuls of mapharsen contains the stated amount of the arsenical, oxophenarsine hydrochloride admixed with anhydrous sodium carbonate, 4.3 per cent and anhydrous sucrose, 81.4 per cent.

U. S. patents 2,092,028 and 2,092,036 (Sept. 7, 1937; expires 1954). U. S. trademark 299,173.

**SULFARSPHENAMINE-U. S. P.**—"Disodium 3,3'-Diamino-4,4'-dihydroxyarsenobenzene-*N*-dimethylenesulfonate. It contains not less than 19 per cent of arsenic (As)." *U. S. P.*

It complies with the requirements of the National Institute of Health of the United States Public Health Service. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Sulfarsphenamine.

*Actions and Uses.*—The same as those of neoarsphenamine; it is probably somewhat more stable in solution in the presence of air, and it permits of intramuscular injection. In terms of percentages there seems to be a higher incidence of reactions following the use of sulfarsphenamine, far more, in fact, than after the use of the other arsenicals employed in the treatment of syphilis. These reactions consist in (a) dermatitis, (b) hemorrhagic eruptions, (c) meningo-vascular reactions, and (d) aplastic anemias. All patients under treatment with sulfarsphenamine should be followed closely by the physician for evidence of reaction. The drug has a place, and may be used by the intramuscular route in the treatment of early heredo-syphilis and in certain cases where the patient has such poor veins that intravenous therapy is out of the question.

*Dosage.*—The maximum dosage by any route should probably not exceed 0.4 Gm., or at most 0.5 Gm. of the dry substance.

For intramuscular or subcutaneous use the drug is dissolved in sterile, freshly distilled water in the proportion of about 0.1 Gm. to 0.3 cc., the total volume being not more than 1.0 to 2.0 cc. There is probably less local reaction where a minimum of diluent is employed. For intravenous use the drug should be diluted in the proportion of 0.1 Gm. to not less than 1.0 and preferably, 4.0 cc., or more, the total volume amounting to 5.0 to 20.0 cc. or more. Dosage for infants is 10 mg. to 15 mg. per kilogram of body weight.

ABBOTT LABORATORIES

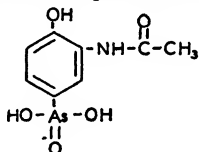
**Sulfarsphenamine:** 0.1 Gm., 0.2 Gm., 0.3 Gm., 0.4 Gm. and 0.6 Gm. ampuls.

MERCK & Co., INC.

**Sulfarsphenamine:** 0.1 Gm., 0.2 Gm., 0.3 Gm., 0.4 Gm., 0.5 Gm. and 0.6 Gm. ampuls.

## Compounds Containing Pentavalent Arsenic

**ACETARSONE-N. F.**—**Stovarsol-Merck.**—3-Acetyl-amino-4-hydroxyphenyl-1-arsonic acid.— $C_8H_{10}O_5AsN$ .—"When dried over sulfuric acid for 3 hours, contains not less than 26.9 per cent and not more than 27.6 per cent of As [arsenic]."—*N. F.*



For description and standards see The National Formulary under Acetarsonic and Acetarsonic Tablets.

**Actions and Uses.**—Acetarsonic has been reported to produce favorable effects in the treatment of amebiasis. Acetarsonic is useful as a means of medication of the vagina in the treatment of *Trichomonas vaginitis*. Its use in the treatment of sarcoid has been recommended by various dermatologists. Acetarsonic has been proposed for use both in prophylaxis and in treatment in certain cases of syphilis, but the evidence is thus far inconclusive. Its use in amebic infections undoubtedly is of value, though still in the experimental stage. In using acetarsonic, the physician should remember that he is working with a rather toxic arsenical preparation, which may give rise to gastrointestinal symptoms and hepatitis as well as to the same cutaneous disturbances that are found with the arsphenamines, for example, urticaria, erythema of various types and even hemorrhagic eruptions. At the least sign of intolerance the physician should discontinue the use of the drug for the time being.

Acetarsonic in common with other arsenicals, should ordinarily not be employed in the presence of hepatitis or kidney damage. Excretion of the administered arsenic is relatively slow; suitable rest periods must therefore be interposed in the treatment to prevent cumulative effects.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endamoeba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa; positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

**Dosage.**—Orally, 0.25 Gm. for adults; two or three doses a day for a period of seven days have been reported to give satisfactory results. For *Trichomonas vaginitis*, use locally in the

vagina a powder containing 12½ per cent acetarsone in a mixture of equal parts of kaolin and sodium bicarbonate. Single dose 4 Gm.—1 teaspoonful of the mixture containing 0.5 Gm. acetarsone. In case of pregnancy, if insufflation is employed, care must be taken to exert no positive pressure in the vagina.

ABBOTT LABORATORIES

**Acetarsone (Powder):** 4 Gm., 20 Gm. and 100 Gm.

**Tablets Acetarsone:** 50 mg., 0.1 Gm., and 0.25 Gm.

ALLEN LABORATORIES, INC.

**Allen Brand Tampon with Acetarsone (Stovarsol):** A lightly compressed stitched tampon of absorbent cotton, coated with 0.1 Gm. of powdered acetarsone, to which is attached a tablet consisting of acetarsone 32 mg. in a tablet base composed of lactose, dextrose, boric acid and starch with a small quantity of sodium bicarbonate and tartaric acid to aid disintegration.

*Actions and Uses.*—(See article on Acetarsone.)

*Dosage.*—Intravaginally, one tampon tablet every other day or daily, followed by a mildly acid douche after a third treatment or after a week's treatment, has been reported to give satisfactory results.

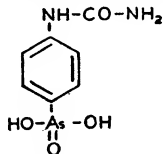
MERCK & Co., INC.

**Stovarsol (Acetarsone) (Powder).**

**Tablets Stovarsol:** 25 mg., 50 mg. and 100 mg.

U. S. trademark 177,082.

**CARBARSONE-U. S. P.**—4-Ureido-1-phenylarsonic acid. —“When dried at 80 C. for six hours, contains not less than 28.1 and not more than 28.8 per cent arsenic (As).”—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Carbarsone and The National Formulary under Carbarsone Tablets.

*Actions and Uses.*—Carbarsone is proposed for the treatment of intestinal amebiasis. It is administered usually by mouth; in acute amebic dysentery or in resistant cases with motile amebas in the stools, retention enemas may be employed. While carbarsone is said to be less toxic than acetarsone and serious untoward effects appear to be uncommon, cutaneous disturbances and other reactions common to arsenic compounds have

been observed. It has been suggested that owing to its chemical structure (in which a modified amido group is para to the arsenic atom, similar to the arrangement in tryparsamide) the administration of carbarsone may lead to injury of the optic nerve. While visual disturbances appear to be quite rare, the possibility of their occurrence should nevertheless be kept in mind during the therapeutic use of the drug. A moderate increase in intestinal activity may be observed. Carbarsone, in common with other arsenicals, should ordinarily not be employed in the presence of hepatitis or kidney damage. Excretion of the administered arsenic is relatively slow; suitable rest periods must therefore be interposed in the treatment to prevent cumulative effects.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endamoeba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa; positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

*Dosage.*—Orally, for adults, the usual dose is 0.25 Gm. twice a day for ten days. If necessary this may be repeated following a ten day rest period. For children, the dosage may be reduced according to weight. As retention enemas, for adults, 2 Gm. of the drug dissolved in 200 cc. of warm 2 per cent sodium bicarbonate solution may be administered following a cleansing alkaline enema every other night for a maximum of five doses, if necessary. Because of the large dosage employed (a total of 10 Gm. over a period of nine days) oral administration should be interrupted during this interval.

ELI LILLY AND COMPANY

**Carbarsone (Powder):** 2 Gm. vial.

**Pulvules Carbarsone:** 0.25 Gm.

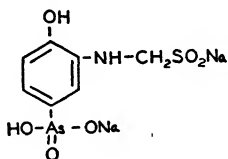
**Suppositories Carbarsone:** 0.13 Gm.

**Tablets Carbarsone:** 50 mg. and 0.25 Gm.

**PHENARSONE SULFOXYLATE.** — Aldarsone-Abbott. — Sodium 3-Amino-4-hydroxyphenylarsonate-N-methanal sulfoxylate.—Phenarsone sulfoxylate consists chiefly of the sodium salt of the pentavalent arsenical compound 3-N-methanal sulfoxylic acid-amino-4-hydroxy phenylarsonic acid, admixed with minor amounts of sodium chloride and sodium bicarbonate incidental to its manufacture. It contains from 17.0 to 18.5 per cent of arsenic. Phenarsone sulfoxylate complies with the



requirements of the National Institute of Health, United States Public Health Service. The probable structural formula of the arsenical compound may be indicated as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Phenarsone sulfoxylate, a pentavalent arsenical, may be used in the treatment of *Trichomonas vaginalis* vaginitis and syphilis of the central nervous system. While this agent probably possesses comparatively low toxic properties, because of its arsenical nature the physician should be on guard against untoward reactions. Such reactions include dermal and hemopoietic changes, nitritoid reactions. Since phenarsone sulfoxylate is a pentavalent arsenic compound, every care should be exercised and visual and color field examinations made prior to drug therapy so that contraction of visual field or symptoms of blurring may be observed.

**Dosage.**—For the treatment of syphilis of the central nervous system, 1 Gm. of phenarsone sulfoxylate dissolved in 10 cc. of sterile distilled water, administered intravenously once a week. The injections may be given continuously for periods of forty to fifty weeks. Concurrent bismuth therapy may be employed during a portion of the course of phenarsone sulfoxylate injection. Phenarsone sulfoxylate may be given as a supplement to fever therapy in the treatment of various forms of central nervous system syphilis.

For the treatment of *Trichomonas vaginalis*, phenarsone sulfoxylate may be administered by insufflation of the powder (with kaolin) and in the form of a suppository. For insufflation the vaginal tract and external os of the cervix are thoroughly cleansed and dried; then the contents of a 3 Gm. vial of phenarsone sulfoxylate with kaolin are introduced by an insufflator. A cautionary statement is issued on the use of positive pressure in the pregnant female when insufflation is employed. The escape of air from the vagina should be permitted during compressions in case the patient is pregnant. The patient is treated for three consecutive days. Then additional treatments are given at three day intervals. No douche should be taken during the treatment.

Phenarsone sulfoxylate suppositories may be used in conjunction with insufflation. They offer a way of providing phenarsone sulfoxylate between insufflation treatments. Suppository treatment is started no sooner than twenty-four hours after the last power treatment. One is inserted every second or third night

until the patient reports for the next insufflation treatment. They may also be used alone by insertion of one suppository every third or fourth night for not more than three weeks. The patient should be warned against prolonged use of this treatment without the advice of a physician, since an arsenical is being employed. Suppositories alone should not be expected to produce permanent results: merely to lessen the discharge and diminish symptoms.

#### ABBOTT LABORATORIES

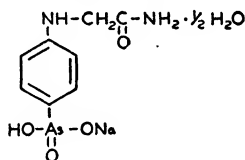
**Aldarsone (Powder):** Phenarsone sulfoxylate 0.5 Gm. and 1 Gm. ampuls.

**Aldarsone with Kaolin:** 3.0 Gm. Each 3.0 Gm. contains phenarsone sulfoxylate 0.5 Gm. and kaolin 2.5 Gm. packaged in glass tubes suitable for use with insufflator.

**Aldarsone Vaginal Suppositories:** Each suppository contains phenarsone sulfoxylate 0.13 Gm. in a glycerogelatin base.

U. S. Patent 2,074,757. U. S. Trademark 338,986.

**TRYPARSAMIDE-U. S. P.**—Monosodium salt of *p*-N-Phenylglycineamidoarsonic Acid.—“When dried to constant weight at 110 C., contains not less than 25.1 per cent and not more than 25.5 per cent of arsenic (As).”—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Tryparsamide.

**Actions and Uses.**—Tryparsamide was first used as a trypanocidal agent especially in the treatment of trypanosomiasis due to *T. gambiense* but is now used as well in resistant cases of syphilis of the central nervous system.

Tryparsamide has some spirocheticidal activity and has an unusual power of therapeutic penetration, especially in case of the central nervous system. The best results seem to have been obtained in patients with early dementia paralytica; it is estimated that perhaps from 40 to 50 per cent of such cases have shown varying degrees of symptomatic improvement. Tabetic affections have responded less satisfactorily, and patients with dementia paralytica with advanced mental and physical deterioration have shown little or no improvement; on the other hand, the drug may hasten the progress of the disease in such cases. Its use is considered inadvisable in forms of syphilis other than

that of the central nervous system. It is being used quite extensively as the follow-up treatment after malaria therapy in syphilis of the central nervous system.

The toxic effects of tryparsamide resemble those of other pentavalent arsenic compounds; the worst of these is the tendency to produce amblyopia, but cases of nitritoid reactions, of jaundice, of agranulocytosis, and of toxic hepatitis have also been reported. Before using the drug, careful consideration should be given to the frequent production of visual injury, which may be serious and permanent. This caution is especially important if the neurosyphilis has involved the optic nerve, causing contraction of the visual and color fields. The drug is, of course, contraindicated in conditions characterized by such contraction. The eyeground fields, including color fields, should always be mapped out before its use is undertaken and should be checked several times thereafter. Sometimes after one or two injections the patient will complain of blurred vision for a few days. In such cases treatment with tryparsamide should be discontinued, the visual fields determined at least weekly for three to four weeks, and then, if there is no evidence of damage to the optic nerve, the injection resumed, using great caution, minimal dosage at first, and checking the visual field preceding each injection. The drug is said to "have no virtues in ophthalmic syphilis."

*Dosage.*—From 1.0 to 3.0 Gm. for adults, depending on the purpose for which the drug is used. In general, the dose should not exceed 0.04 to 0.05 Gm. per kilogram of body weight, and such doses should not be repeated at intervals of less than one week. Tryparsamide is employed by the intravenous route. The drug is dissolved in sterile water or physiologic solution of sodium chloride. Tryparsamide should never be administered by mouth.

MERCK & Co., INC.

**Tryparsamide (Powder):** 50 Gm. bottle and 1 Gm., 2 Gm. and 3 Gm. ampuls.

U. S. patents 1,280,119, 1,280,120, 1,280,121, 1,280,122, 1,280,123, 1,280,124 and 1,280,126 (Sept. 24, 1918; expired) by license of the Rockefeller Institute for Medical Research. U. S. trademark 186,022 (expired).

### Bismuth Compounds

Until 1921 bismuth had been used particularly in the treatment of intestinal infections, as a paste for tuberculous fistulae and in radiology. Sauton and Robert then showed the value of sodium potassium bismuth tartrate in trypanosomiasis and spirillosis of fowls. Sazerac and Levaditi then took up the treatment of syphilis with the same drug. From this time on the value of bismuth preparation for treating syphilis has been realized more and more and its general use has been increased

enormously throughout the world. Bismuth seems to have both a spirocheticidal and a spirochetostatic effect.

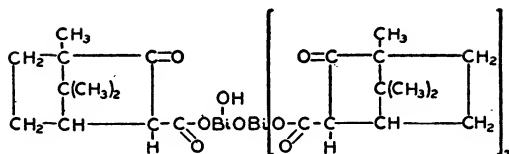
Thus far the best results with bismuth therapy of syphilis have been achieved by intramuscular injection. Probably those compounds of bismuth will have the best spirocheticidal value that are able to keep the therapeutic level of bismuth in the blood stream at such a continuous height that it will be reflected in the urine with a level of 0.002 Gm. or more of metallic bismuth per day. Intravenous injections are strictly contraindicated for the reason that the therapeutic dose approaches too closely to the toxic dose. The compounds employed for intramuscular injection consist of water soluble salts dissolved in aqueous solution or other suitable solvents, or suspended in oils; of insoluble bismuth salts suspended in water or oils; of so-called oil soluble preparations; of water soluble and oil suspended combinations; and finally of bismuth and arsenic compounds. The so-called oil soluble preparations are claimed to be more exact in their dosage and to be absorbed more rapidly than insoluble suspensions of bismuth salts. They are said not to be absorbed and excreted so rapidly as the soluble bismuth preparations. Thus, they combine some of the advantages of both the soluble and of the insoluble preparations. This question has not been entirely and satisfactorily answered as yet. Thus far it seems to be the generally accepted opinion that bismuth salts used in the treatment of syphilis should be administered by the intramuscular route. In intramuscular injections of the bismuth salts the needle should be inserted in the upper and outer quadrant of the gluteal region near the inner angle of the quadrant. Having the syringe tip firmly inserted into the butt of the needle, the physician should hold the syringe loosely between the thumb and first finger, much like holding a pencil. The skin of the buttock is drawn down a little with the left hand and then with a free back and then forward motion of the right hand the needle (pointed upward and slightly toward the median plane at an angle of about 70° with the skin) is boldly plunged, not pushed, deep into the muscular tissue. With the needle still in place the physician should then aspirate back with the plunger of the syringe several times in order to be sure that the needle is not in a vein or in an artery. This having been ascertained the needle butt is held firmly in place with the thumb and first finger of the left hand while the injection is made with the right hand. This will go far toward obviating many of the distressing venous emboli and arterial emboli that have been reported. Those who have worked with bismuth salts in treating syphilis believe that their efficiency stands between that of mercury and that of arsphenamine. The present evidence appears to show that there is warrant for the administration of bismuth compounds in the treatment of syphilis in connection with arsphenamine or as a substitute for mercury therapy. Some few syphilologists use bismuth therapy alone in treatment of syphilis. These men are much in the minority, however. Bismuth compounds are most

valuable in the treatment of syphilis in patients who are intolerant to other drugs or who show resistance to other drugs used in syphilis, e.g., the arsenic-fast individual, or so-called arsenic-intolerant individual. However, there is far more chance of curing a patient with syphilis where the physician is able to use both arsenical therapy and bismuth therapy, either in alternating courses or, in certain instances, in a combined fashion. Treatment with bismuth preparations is not usually injurious if the necessary precautions are taken (careful observation of the skin for untoward reaction, of the mouth for signs of beginning bismuth stomatitis and of the urine for evidence of irritation of the kidneys).

Bismuth may be used for the treatment of all forms of syphilis, including neurosyphilis and cardiovascular syphilis. It should be emphasized that bismuth, alone or in combination with arsenicals, cannot be considered curative in the more advanced forms of neurosyphilis such as paresis. Furthermore, there is evidence that penicillin alone or combined with fever therapy, may prove to be superior to either the arsenicals or bismuth in the treatment of neurosyphilis. It is as yet too early to state the precise relative therapeutic efficacy of the various agents employed in this condition, but all are considered to be of value.

In common with another heavy metal, mercury, bismuth preparations when administered by injection, have a definite diuretic action. Excretion studies of various bismuth compounds used in the treatment of syphilis give some indications as to the best type of bismuth salts for desired results. The usefulness of a bismuth preparation involves the concentration of active bismuth attained in the tissues, especially in the blood, and the height, course, rise, duration and decline of this concentration. As a rule, water solutions, if repeated often enough, give a rapid and important absorption of the metal and a sustained high concentration in the blood stream. This can be kept up if the injections are given frequently enough, i.e., two or three times a week. Oil suspensions differ in that there is a slower absorption and concentration in the blood stream, but one which persists longer, thus requiring injections but once a week. Certain of the oil solutions have like characteristics, with an added more rapid absorption than the oil suspension. Bismuth subsalicylate is more slowly absorbed and there is a somewhat longer delay before the bismuth effect is achieved. Moreover, in small amounts it continues to be excreted over long periods of time, even months after injections are stopped. Whether this long excretion indicates a therapeutic level of the drug in the body is doubtful.

**BISMUTH CAMPHOCARBOXYLATE.**—Bismo-Cymol-Abbott.—A basic bismuth salt of camphocarboxylic acid (camphor-3-carboxylic acid) having the probable structural formula shown below. It contains between 37 and 40 per cent of bismuth. The formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Bismuth camphocarboxylate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see article on Bismuth Compounds). Bismuth camphocarboxylate belongs to the class of so-called liposoluble bismuth compounds which, because of their solubility, are absorbed more rapidly than insoluble bismuth salts, approaching that of soluble bismuth salts. Though animal experiments seem to show a low toxicity for this preparation, in human beings it is well to watch the gums closely for evidence of beginning stomatitis.

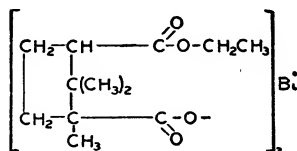
**Dosage.**—Bismuth camphocarboxylate is injected intramuscularly in doses representing 0.1 Gm. of metallic bismuth once a week or in doses representing 50 mg. of metallic bismuth twice a week for from eight to ten weeks.

#### ABBOTT LABORATORIES

**Solution Bismo-Cymol:** 2 cc. ampuls and 60 cc. Each cc. contains bismo-cymol equivalent to 50 mg. of metallic bismuth, dissolved in olive oil.

U. S. patent 1,921,638 (Aug. 8, 1933; expires 1950). U. S. trademark 277,960.

**BISMUTH ETHYLCAMPHORATE.**—The bismuth III salt of *d*-camphoric acid mono-ethyl ester. It may be prepared by the interaction of sodium ethylcamphorate and bismuth nitrate in dilute aqueous glycerin solution. The product may then be extracted with chloroform and recovered by the removal of that solvent. It possesses the following formula:



For tests and standards, see Section B.

It may be prepared by the interaction of sodium ethylcamphorate and bismuth nitrate in dilute aqueous glycerin solution. The product may then be extracted with chloroform and recovered by the removal of that solvent.

**Actions and Uses.**—Bismuth ethylcamphorate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis. It is a liposoluble compound not so readily absorbed as the water soluble preparation and yet more rapidly absorbed than the suspensions of insoluble bismuth salts in oil. Injection intramuscularly of this preparation produces relatively little local reaction.

**Dosage.**—For the average adult, 2 cc. (80 mg. of metallic bismuth), administered once a week for a series of ten to fifteen injections.

#### THE UPJOHN COMPANY

**Solution Bismuth Ethylcamphorate in Oil with Benzyl Alcohol 2.5%:** 1 cc. and 2 cc. ampuls and 30 cc. vials. Each cubic centimeter of solution contains a suspension of bismuth ethylcamphorate equivalent to 40 mg. of elemental bismuth, camphor 0.10 Gm. and benzyl alcohol 0.025 cc., dissolved in vegetable oil.

**BISMUTH POTASSIUM TARTRATE-U. S. P.**—Potassium Bismuth Tartrate.—“Contains the equivalent of not less than 60 per cent and not more than 64 per cent of Bi [bismuth].”—U. S. P.

For description and standards see the U. S. Pharmacopeia under Bismuth Potassium Tartrate and Bismuth Potassium Tartrate Injection.

**Actions and Uses.**—It is used for the antisypilitic effects of bismuth. See general article, Bismuth Compounds.

**Dosage.**—(a) Oily Suspension.—From 0.1 to 0.2 Gm. by intramuscular injection, preferably into the gluteal muscle. The injections may be repeated at intervals of seven days until a total of from 2.4 to 3.0 Gm. has been given. (b) Aqueous Isotonic Solution.—50 mg. by intramuscular injection, preferably into the gluteal muscles, three times a week, until a total of 12 to 18 injections has been given.

#### ABBOTT LABORATORIES

**Suspension Bismuth Potassium Tartrate in Oil with Butyn 0.4%:** 2 cc. ampuls. Each ampul contains bismuth potassium tartrate, 0.2 Gm. and Butyn 0.4 per cent with Metaphen 1:20,000 suspended in peanut oil.

**Solution Bismuth Potassium Tartrate 2.5% with Benzyl Alcohol 2%:** 60 cc. bottle. Bismuth potassium tartrate, 2.5 per cent in an aqueous solution containing benzyl alcohol 2 per cent, and sucrose 6 per cent.

**Suspension Bismuth Potassium Tartrate in Oil 10% with Butyn 0.4%:** 60 cc. bottle. Each cc. contains Bismuth potassium tartrate 0.1 Gm. (equivalent to 62 mg. elemental bismuth), Butyn 0.4 per cent and Metaphen 1:20,000 suspended in peanut oil.

BREWER & CO., INC.

**Solution Bismuth Potassium Tartrate:** 2 cc. ampuls. Each ampul contains bismuth potassium tartrate 50 mg. with benzyl alcohol 0.04 Gm.

**BISMUTH SODIUM TARTRATE.**—A basic sodium bismuth tartrate containing from 72.7 to 73.9 per cent of bismuth.

For tests and standards, see Section B.

*Actions and Uses.*—Bismuth sodium tartrate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (See general article, Bismuth Compounds). The drug has a definite diuretic action.

*Dosage.*—30 mg. by intramuscular injection, preferably into the gluteal muscle. The initial dose is 15 mg., increased to 30 mg. with the second dose and continued in three doses weekly for from six to ten weeks.

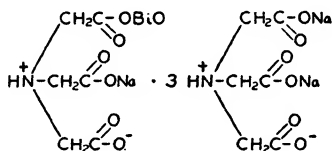
G. D. SEARLE & CO.

**Solution Bismuth Sodium Tartrate, 1.5% with Benzyl Alcohol 2%:** 2 cc. ampul and 60 cc. vial. An aqueous solution containing bismuth sodium tartrate 30 mg., benzyl alcohol 40 mg. and sucrose 0.50 Gm., in 2 cc.

**Solution Bismuth Sodium Tartrate, 3% with Benzyl Alcohol 2%:** 2 cc. ampuls and 60 cc. vial. An aqueous solution containing bismuth sodium tartrate 30 mg., benzyl alcohol 20 mg. and sucrose 0.25 Gm., in one cubic centimeter.

U. S. patents 1,663,201 (March 20, 1928; expired), and 1,801,433 (April 21, 1931; expires 1948).

**BISMUTH SODIUM TRIGLYCOLLAMATE.**—Bis-trimate-C. D. Smith.—A double salt of sodium bismuthyl triglycollamate and disodium triglycollamate containing approximately 18.3 per cent of bismuth. The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Bismuth sodium triglycollamate is designed to provide bismuth in a form effective for oral administration in the treatment of syphilis. It may be used as an adjunct with arsenicals or other agents shown to be effective in the treatment



of the disease. It may be used alone in the management of certain forms of the disease, but it should not be solely relied upon for curative therapy of early or active syphilitic infection. It is primarily indicated when there is intolerance to other drugs or other forms of bismuth ordinarily employed for the same purpose.

Bismuth sodium triglycollamate is subject to the same contraindications of bismuth preparations in general and should be discontinued in the presence of nephritis upon the appearance of albuminuria.

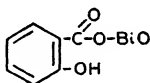
**Dosage.**—Bismuth sodium triglycollamate is administered orally in tablet form, usually prescribed in single doses of 0.41 Gm. (75 mg. of bismuth) two or three times daily after meals to provide a total daily dosage of from 0.82 Gm. (150 mg. of bismuth) to 1.23 Gm. (225 mg. of bismuth). The higher total daily dosage is desirable to maintain a satisfactory bismuth excretion level, but this may be temporarily reduced to the lower figure to overcome gastro-intestinal disturbances that are occasionally encountered.

CARROLL DUNHAM SMITH PHARMACAL CO.

**Tablets Bistrimate:** 0.41 Gm. Each tablet contains the equivalent of 75 mg. of bismuth.

U. S. patent 2,348,984.

**BISMUTH SUBSALICYLATE-U. S. P.**—Basic Bismuth Salicylate.—“A basic salt, which, when dried over sulfuric acid for 18 hours, yields upon ignition not less than 62 per cent and not more than 66 per cent of  $\text{Bi}_2\text{O}_3$ .”—U. S. P. The structural formula may be represented as follows:



For description and standards, see the U. S. Pharmacopeia under Bismuth Subsaliolate and Bismuth Subsaliolate Injection.

**Actions and Uses.**—The oral administration of bismuth subsalicylate has apparently found little application, and it is probably decomposed in part with the liberation of salicylic acid in the presence of the gastric juice. Its chief use is in the treatment of syphilis for which purpose it is suspended in oil and is injected intramuscularly. It is absorbed slowly and irregularly after intramuscular injection and is excreted mainly through the kidney. The rate of elimination following a single intramuscular dose reaches the maximum in about 11 or 12 days, and with repeated intramuscular injections the maximum is reached in about 19 to 21 days, after which the rate of excretion remains fairly constant for some time. See general article, Bismuth Compounds.

**Dosage.**—Gastro-intestinal, 1 Gm. Antisyphilitic, by parenteral

injection, 0.125 Gm. The drug is suspended in oil and injected intramuscularly once a week until (a course of) from eight to twelve doses have been injected.

**ABBOTT LABORATORIES**

**Suspension Bismuth Subsalicylate in Oil with Chlorobutanol 3% :** 1 cc. ampuls; 30 cc. and 60 cc. bottles. A suspension of bismuth subsalicylate in a mixture of peanut oil and ethyl esters of olive oil fatty acids containing in each cubic centimeter 0.13 Gm. of bismuth subsalicylate and chlorobutanol 3 per cent.

**Suspension Bismuth Subsalicylate in Oil with Chlorobutanol 3% :** 0.13 Gm. in 1 cc. ampuls. A suspension of bismuth subsalicylate in olive oil containing in each cubic centimeter 0.13 Gm. of bismuth subsalicylate and chlorobutanol 3 per cent.

**Suspension Bismuth Subsalicylate in Oil with Chlorobutanol 3% :** 30 cc., 60 cc., 100 cc. and 480 cc. bottles. A suspension of bismuth subsalicylate in olive oil containing in each cubic centimeter 0.13 Gm. of bismuth subsalicylate and chlorobutanol 3 per cent.

**DIARSENOL COMPANY, INC.**

**Suspension Bismuth Subsalicylate in Oil with Chlorobutanol 3% :** 30 cc., 60 cc., and 100 cc. bottles. A suspension of bismuth subsalicylate in peanut oil, each cubic centimeter containing 0.13 Gm. of bismuth subsalicylate (equivalent to 75 mg. of Bi metal) and 30 mg. (3 per cent) of chlorobutanol.

**THE DRUG PRODUCTS CO., INC.**

**Suspension Bismuth Subsalicylate in Oil with Chlorobutanol 3% :** 60 cc. hypodermic. This multiple dose vial contains in each cubic centimeter bismuth subsalicylate 0.13 Gm., chlorobutanol anhydrous 30 mg. and olive oil q. s.

**ENDO PRODUCTS, INC.**

**Suspension Bismuth Subsalicylate in Oil with Chlorobutanol 3% :** 2 cc. ampuls. A suspension of bismuth subsalicylate in peanut oil containing in each cubic centimeter bismuth subsalicylate U. S. P. equivalent to 50 milligrams to 60 milligrams of bismuth with 3 per cent of chlorobutanol.

**Suspension Bismuth Subsalicylate in Oil with Chlorobutanol 3% :** 20 cc., 60 cc. and 100 cc. bottles. A suspension of bismuth subsalicylate in peanut oil containing in each cubic centimeter bismuth subsalicylate U. S. P. equivalent to 50 milligrams to 60 milligrams of bismuth with 3 per cent chlorobutanol.

**MERCK & CO., INC.**

**Bismuth Subsalicylate (Powder):** bulk.

## PARKE, DAVIS AND COMPANY

**Suspension Bismuth Salicylate in Oil with Chloretone** 3% : 30 cc., 60 cc. and 500 cc. bottles. A suspension of bismuth subsalicylate in peanut oil, containing 3 per cent of chlorobutanol. Each cubic centimeter contains bismuth subsalicylate, 0.13 Gm.

**Suspension Bismuth Salicylate in Oil with Chloretone** 3% : 0.13 Gm. in 1 cc. ampuls. Each ampul contains 1 cc. of a suspension of bismuth subsalicylate 0.13 Gm., in peanut oil, containing 3 per cent of chlorobutanol.

## THE SMITH-DORSEY CO.

**Suspension Bismuth Subsalicylate in Oil with Chlorobutanol** 3% : 50 cc. vials. A suspension of bismuth subsalicylate in peanut oil containing in each cubic centimeter bismuth subsalicylate 0.13 Gm. with 3 per cent chlorobutanol added.

## THE UPJOHN COMPANY

**Suspension Bismuth Subsalicylate in Oil with Chlorobutanol** 3% : 1 cc. ampuls and 30 cc. vials. Each cubic centimeter contains bismuth subsalicylate 0.13 Gm. and chlorobutanol 30 mg. suspended in vegetable oil.

**IODOBISMUTHITE SODIUM.**—Bismuth Sodium Iodide.—A compound formed by the interaction of bismuth chloride and sodium iodide in ethyl acetate solution, consisting essentially of hydrated sodium iodobismuthite (bismuth sodium iodide)  $\text{Na}_2\text{BiI}_5$ , with inorganic salts. It contains approximately 21 per cent bismuth (Bi), 62 per cent iodide (I<sup>-</sup>) and 11 per cent water of hydration.

For tests and standards, see Section B.

*Actions and Uses.*—It is claimed for iodobismuthite sodium that it has the quality of appearing in the spinal fluid and of penetrating the brain tissue. This claim and therapeutic indications based upon it require further confirmation.

*Dosage.*—See Iodobismutol with Ethyl Aminobenzoate.

**IODOBISMUTHITE SODIUM WITH ETHYL AMINOBENZOATE.**—Iodobismutol with Benzocaine-Squibb.—A solution of sodium iodobismuthite (bismuth sodium iodide) and sodium iodide in propylene glycol containing ethyl aminobenzoate.

For tests and standards, see Section B.

*Actions and Uses.*—Iodobismuthite sodium with ethyl aminobenzoate seems to be well absorbed and to be excreted fairly rapidly. Intramuscular injections twice weekly produce a satisfactory therapeutic bismuth level in the blood stream as reflected in the sustained excretion level in the urine.

*Dosage.*—Intramuscular injections of 2 cc. repeated every three days. Two full days should elapse between injections.

From sixteen to twenty injections comprise a course of treatment. In case of arsenical sensitization such therapy may be continued over a long period of time. At each injection the patient would thus receive from 0.024 to 0.0276 Gm. of metallic bismuth (from 0.1154 to 0.1328 Gm. of sodium bismuth iodide, and from 0.218 to 0.258 Gm. of sodium iodide).

E. R. SQUIBB & SONS

**Solution Iodobismitol with Benzocaine:** 2 cc. ampuls and 50 cc. rubber capped bottles. Each 2 cc. contains iodobismuthite sodium 0.12 Gm., sodium iodide 0.24 Gm., ethyl aminobenzoate 80 mg., propylene glycol q. s. 2 cc.

U. S. patent 1,927,210 (Sept. 19, 1933; expires 1950).

**POTASSIUM SODIUM BISMUTHYL TARTRATE.**

—A basic water soluble potassium sodium bismuth tartrate containing from 40.75 to 41.25 per cent of bismuth.

For tests and standards, see Section B.

*Actions and Uses.*—Potassium sodium bismuthyl tartrate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (See general article, Bismuth Compounds).

**QUININE BISMUTH IODIDE.**—A substance of variable composition containing between 18 and 20.1 per cent of bismuth, between 48.7 and 53.5 per cent of iodine; and quinine.

For tests and standards, see Section B.

*Actions and Uses.*—Quinine bismuth iodide is proposed as a means of obtaining the systemic effect of bismuth in the treatment of syphilis (See general article, Bismuth Compounds).

**SOBISMINOL MASS.**—A complex organic bismuth product the chemical nature of which has not been fully established. It is obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol. It contains between 19.25 and 20.25 per cent of bismuth; 0.75 Gm. of sobisminol mass represents 150 mg. of bismuth.

For tests and standards, see Section B.

*Actions and Uses.*—Sobisminol mass is proposed in the treatment of syphilis and is intended for use by the oral route. It is particularly indicated for those patients unable to undergo intramuscular bismuth therapy and to supplant therapy by that route for patients compelled for a time to be out of contact with their physician. Again it may be indicated in certain other types of syphilis, e.g. congenital and latent syphilis. It is to be emphasized that it is too dangerous a drug to be employed by the patient without the careful supervision and direction of his physician, and it is sold only on prescription. In the first few days of therapy the patient should be carefully supervised and later watched for evidence of gastro-intestinal upsets and of bismuth intoxication.

Absorption of sobisminol (mass or solution) appears to be rapid and sufficient to maintain an effective antisyphilitic level of bismuth concentration in the body. An adequate amount of sobisminol mass by mouth can be expected to result in a curve for urinary excretion resembling closely in course and degree those given by intramuscular injection of the water soluble and oil soluble compounds. The oral dose has to be considerably higher than the intramuscular dose of sobisminol. Further, intramuscular injections of sobisminol solution results in greater urinary excretion than is obtained by oral administration. Daily urinary excretion of bismuth compounds fluctuates considerably, but excretion continues for many days.

The toxicity of sobisminol compares favorably with that of other water soluble bismuth compounds used in the treatment of syphilis. Side effects appear to be usually of a relatively transient nature. They include nausea, vomiting, burning sensations in the esophagus, diarrhea, stomatitis and bismuth line. There appears to be no tendency to cumulative toxic effects.

*Dosage.*—Adult dosage, from two to three capsules three times a day, taken with plenty of water, at 10 a. m., 3 p. m. and 8 p. m. Each capsule represents 150 mg. of metallic bismuth. Unless contraindications arise, such therapy may be continued for from ten to twelve weeks and represents a course of bismuth therapy. For children the dosage may be cut down to one capsule three times a day, or a 75 mg. capsule three times a day for a young child.

ELI LILLY AND COMPANY

**Pulvules Sobisminol Mass: 0.75 Gm.**

**BISMUTH SODIUM THIOGLYCOLLATE**—Thio-Bismol-Parke, Davis.—Bismuth sodium thioglycollate.—A salt formed by the interaction of sodium thioglycollate and bismuth hydroxide. The product has the general formula  $\text{Bi}(\text{SCH}_2\text{CO}_2\text{Na})_3$ , though it may differ slightly in composition from this formula. It contains approximately 38 per cent of bismuth.

For tests and standards, see Section B.

*Actions and Uses.*—Bismuth sodium thioglycollate is proposed as a means of obtaining the systemic effects of bismuth in the treatment of syphilis (see general article, Bismuth Compounds); it is a water-soluble compound, readily absorbable, and produces relatively little local injury. A single injection of 0.1 to 0.2 Gm. has a definite effect in temporarily stopping the course of a therapeutic malaria.

*Dosage.*—For the average adult, 0.2 Gm. administered intramuscularly three times a week for a series of from twelve to fifteen doses.

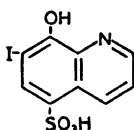
PARKE, DAVIS & COMPANY

**Thio-Bismol: 0.2 Gm. and 2 Gm. ampuls.**

U. S. trademark 220,808.

*Chiniofon*

**CHINIOFON-U. S. P.**—"A mixture of 7-iodo-8-hydroxyquinoline-5-sulfonic acid, its sodium salt, and sodium bicarbonate, containing not less than 26.5 and not more than 29 per cent of iodine (I)."—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Chiniofon and Chiniofon Tablets.

*Actions and Uses.*—Chiniofon, which is closely similar to preparations introduced under various proprietary names as wound antiseptics, has been found to be of use in the treatment of amebic dysentery. It is claimed that the action of the drug is probably due to its absorption and direct action through the blood stream on the amebas invading the bowel wall. The drug has been reported in some cases to produce diarrhea; but serious toxic effects do not appear to be common.

The diagnosis of amebiasis depends on the observation of motile forms or cysts of *Endameba histolytica* in stool specimens (repeated examinations are often necessary) or their recovery by means of the proctoscope from the intestinal mucosa; positive diagnosis can often be made by the latter procedure when stool examinations are negative, and this is considered to be the more satisfactory as well as the more rapid method of diagnosis in many cases. It is important that negative findings should be checked by stool cultures.

In view of the frequency of persistent infection in the absence of marked symptoms, adequate therapy includes reexaminations and repetitions of courses of treatment.

*Dosage.*—Orally, for adults, from 0.25 to 1.0 Gm. in the form of pills, cachets or solutions, three times daily; for children, according to age; rectally, 1 to 5 Gm. freshly dissolved in 200 cc. of water at a temperature not exceeding 44 C. The course of treatment requires from seven to fourteen days. Combined oral and rectal administration has been used in acute cases and in the more serious chronic cases accompanied by obstinate clinical symptoms. It has been pointed out that the iodine content of chiniofen should be considered when chronic endamebiasis is accompanied by thyroid disturbance.

Until more evidence becomes available, chiniofon should be used with caution in cases with liver damage.

## ABBOTT LABORATORIES

**Enterab Tablets Chiniofon:** 0.25 Gm. Each tablet is enteric coated with a resin prepared from stearic acid, phthalic anhydride and glycerin.

U. S. trademark 353,674.

## ERNST BISCHOFF CO.

**Anayodin (Powder):** 25 Gm. and 100 Gm. bottles.

**Pills Anayodin:** 0.25 Gm., enteric coated with shellac and magnesium stearate.

U. S. patent 232,215.

## ENDO PRODUCTS, INC.

**Chiniofon (Powder):** 30 Gm. bottles.

**Tablets Chiniofon (Enteric Coated):** 0.25 Gm.

## PREMO PHARMACEUTICAL LABORATORIES, INC.

**Chiniofon Enerels:** 0.25 Gm. tablets coated with shellac.

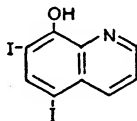
## WINTHROP-STEARN, INC.

**Chiniofon (Powder):** bulk.

**Tablets Chiniofon:** 0.25 Gm. The tablets are coated with keratin.

## Iodine Compounds

**DIIDO - HYDROXYQUINOLINE — Diodoquin-Searle — Yodoxin-Lemke.** — 5,7-di-Iodo-8-hydroxyquinoline,  $C_9H_4N.OH.I_2$ .—A compound resulting from the introduction of two atoms of iodine into 8-hydroxyquinoline. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Diodo-hydroxyquinoline is used as an antiprotozoan agent for use in amebic dysentery and in the treatment of *Trichomonas hominis* (intestinalis) infections.

**Dosage.**—Adults—seven to ten tablets a day for fifteen to twenty days.

## B. L. LEMKE &amp; Co., INC.

**Yodoxin (Powder):** 25 Gm., 100 Gm. and 454 Gm. bottles and in bulk.

**Tablets Yodoxin:** 210 mg.

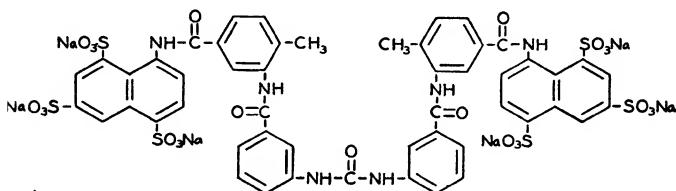
G. D. SEARLE & Co.

Tablets Diodoquin: 0.21 Gm.

U. S. trademark 336,484.

### Urea Derivative

**SURAMIN SODIUM-U. S. P.—Naphuride Sodium-Winthrop-Stearns.** — Hexa-sodium bis-(*m*-aminobenzoyl-*m*-amino-*p*-methylbenzoyl-1-naphthylamino-4,6,8-trisulfonate) carbamide.—The structural formula of suramin sodium may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Suramin Sodium.

**Actions and Uses.**—Suramin sodium is a trypanosomicide which readily dissolves in sterile water; the solution is neutral in reaction, odorless and almost tasteless. Only freshly made solutions should be employed. It is slowly eliminated and remains active in the body for a considerable period, offering several months' protection against reinfection with the trypanosomes of both forms (Gambien and Rhodesian) of African sleeping sickness. It is claimed to produce excellent results in the first stage of trypanosomiasis and a favorable influence in the second stage of the disease. It is said to be of particular value in the prophylaxis of sleeping sickness. While the drug is relatively safe when properly used, it exerts an irritant action on the kidney; even after comparatively small doses there is frequent occurrence of albumin and sometimes hyaline and granular casts and red blood cells in the urine. However, albuminuria generally disappears spontaneously in about six weeks. The drug should be used only with great caution in patients with renal insufficiency and albuminuria, since severe nephritis, amblyopia, amaurosis and anuria have been noted. In larger doses suramin sodium may have a hemolytic action. Occasionally dermatitis, chill, fever, headache, nausea and pruritus may be noticed, and more rarely conjunctivitis, stomatitis, cutaneous hemorrhages, globinuria and agranulocytosis. Since the compound is slowly eliminated and has a cumulative action, side effects may appear after cessation of treatment. The drug should not be continued in patients who show intolerance to initial doses. During treatment daily urinalysis and determination of blood pressure has been suggested, as have frequent complete blood counts, de-



termination of nonprotein nitrogen content of the blood, and determination of the potassium, sodium and chloride content of the blood, so that degeneration of the adrenal cortex, if it occurs, may be detected early.

**Dosage.**—Suramin sodium is usually administered intravenously in a freshly prepared 10 per cent solution. If a venipuncture is impossible, the solution may be injected intramuscularly. During the preparation of a solution, the powder is sprinkled to avoid formation of clumps on the surface of sterile distilled water. In the treatment of African sleeping sickness, the average single dose for adults is claimed to be 1 Gm. and the total dose from 5 to 10 Gm., 1 Gm. being given at weekly intervals. Some administer 1 Gm. on consecutive or on alternate days for three doses, followed by 1 Gm. weekly for from two to seven additional doses, so that the total dose is from 5 to 10 Gm. Combined treatment with suramin sodium and tryparsamide has also been recommended, since cases with invasion of the central nervous system, as may occur early in the disease, are favorably influenced by the arsenical.

For the prophylaxis of African sleeping sickness the dose for adults is 1 Gm., for children from 0.3 to 0.75 Gm. and for infants from 0.15 to 0.2 Gm. The same dose is repeated in a week. At the expiration of three months, but not before, a similar prophylactic procedure may be followed.

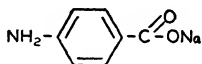
WINTHROP-STEARN, INC.

**Naphuride Sodium:** 1 Gm. ampuls.

U. S. patent 1,218,655 (March 13, 1917; expired); 1,308,971 (July 1, 1919; expired). U. S. trademark 398,172.

### Antirickettsial Agent

**SODIUM PARA-AMINO BENZOATE.**—The sodium salt of *para*-aminobenzoic acid.—The structural formula of sodium *p*-aminobenzoate may be represented as follows:



For tests and standards, see Section B.

Sodium *p*-aminobenzoate, when dried at 110 C. for three hours, contains not less than 98 per cent of  $\text{NaC}_7\text{H}_6\text{O}_2\text{N}$ .

**Actions and Uses.**—Sodium *para*-aminobenzoate has been found to exert a depressant action on the metabolism of Rickettsiae that is useful for the management of certain rickettsial diseases. It is reported to be of value in the treatment of Rocky Mountain spotted fever, epidemic and endemic (murine) typhus, and in tsutsugamushi disease (scrub typhus). It has not proved uniformly successful in the treatment of all rickettsial infections so that its ultimate value in other typhus fevers or rickettsial

diseases remains to be determined. Its use as a prophylactic is not recommended until more is known of its long term toxic effects in man and its ultimate protective value when administered routinely to individuals in endemic areas.

Sodium *para*-aminobenzoate should not be administered in conjunction with the sulfonamides because of the well known inhibitory effect of *para*-aminobenzoic acid upon the antibacterial effect of these agents. It is not antagonistic to penicillin.

**Dosage.**—Sodium *para*-aminobenzoate is administered orally in tablet form. The recommended average adult initial therapeutic dose is 4 to 6 Gm.; this may be followed by doses of 2 to 3 Gm. every two hours. Within the first 24 hours of therapy with *para*-aminobenzoic acid in rickettsial diseases, concentrations of 30 to 40 milligrams per cent of the drug should be obtained and then maintained in the blood of the patient. If definite improvement is not noted within 48 hours, increase the dose of the drug to a point which will produce a concentration of 40 to 50 milligrams per cent of *para*-aminobenzoic acid in the blood of the patient. Levels above 60 milligrams per cent of the drug may be dangerous, because *para*-aminobenzoic acid is not a completely innocuous agent as it may produce hepatic and renal lesions. Blood levels range 30 to 60 mg. per 100 cc., but since this seems to be more a function of the urine output than the dosage, this is usually limited to 500 cc. per day by restriction of fluid intake. Until more is known concerning the possible toxicity of the drug in man the administration of a daily dosage in excess of 30 Gm. for a period of more than one week is not recommended.

INTERNATIONAL VITAMIN DIVISION, IVES CAMERON CO., INC.

Tablets Sodium Paba: 0.5 Gm.

WYETH, INCORPORATED

Tablets Sodium Paba: 0.5 Gm.

U. S. patent 2,403,473.

### Anthelmintic Agent

#### CARBON TETRACHLORIDE-N. F.— $\text{CCl}_4$ .

For description and standards see The National Formulary under Carbon Tetrachloride and Carbon Tetrachloride Capsules.

**Actions and Uses.**—Carbon tetrachloride has narcotic and anesthetic properties somewhat similar to those of chloroform. It has come into use as a vermifuge in the treatment of hookworm disease. It is reported that usually about 95 per cent of the hookworms are removed by the first dose of carbon tetrachloride and that occasionally all are removed. As a vermifuge it appears to be relatively safe, but serious symptoms and even death have occurred, especially in patients addicted to the use of alcohol. During treatment some of the patients complain of headache. Good results are obtained by administration in water

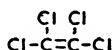
or milk or in gelatin capsules on an empty stomach, followed in three hours by a purgative dose of magnesium sulfate. The capsules may be prepared extemporaneously. Lambert recommends giving the vermicide and a solution of magnesium sulfate together, claiming that this prevents headache. A mild laxative is generally given to constipated patients on the day previous to treatment. To insure complete removal of the hookworms a test dose of oil of chenopodium, 3 cc. (45 minims), may be given a week after the treatment with carbon tetrachloride. A second dose of carbon tetrachloride should not be given within three weeks. Alcohol should not be taken during treatment.

*Dosage.*—From 2 to 3 cc.; the dose of 3 cc. should not be exceeded. For children 0.13 cc. for each year of age up to 15 years. The capsules should be swallowed immediately, not broken in the mouth. A purgative dose of magnesium sulfate is administered two or three hours after the anthelmintic. A laxative dose of the salt should be administered also on the preceding day.

MERCK & Co., INC.

**Carbon Tetrachloride (*Liquid*):** bulk.

**TETRACHLOROETHYLENE—U. S. P.**—Perchloroethylene.—“Contains not less than 99 per cent and not more than 99.5 per cent of  $C_2Cl_4$ , the remainder consisting of alcohol.” *U. S. P.* The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Tetrachloroethylene and Tetrachloroethylene Capsules.

*Actions and Uses.*—Observations of many workers have shown that tetrachlorethylene is a useful anthelmintic for the treatment of hookworm infestation. It has been used against other worms with less success, although there is some evidence that it is useful in *Trichuris* infestation. It may be lethal to *Ascaris* but its use in that infestation is not advised because of the danger of causing migration of the worms. It is the consensus of the investigators that tetrachlorethylene is less toxic than carbon tetrachloride ( $CCl_4$ ) and at least as efficacious as the latter drug. It has a further advantage over carbon tetrachloride in that it does not raise the guanidine content of the blood, which is important in cases exhibiting a calcium deficiency. Untoward reactions are rare, but giddiness, vomiting and drowsiness have been reported in some cases. It is probably better to keep the patient (especially children) in bed during the treatment.

*Dosage.*—From 1 to 3 cc., depending on the age of the patient. Tetrachlorethylene is usually given in soft gelatin capsules but

has also been administered to children on a lump of sugar. The gastro-intestinal tract should be thoroughly emptied before administering tetrachlorethylene. Fats and alcohol must be avoided, because they favor absorption of the drug. A dose of tetrachlorethylene should be followed by a saline cathartic of sodium or magnesium sulfate. One dose frequently suffices, but if necessary it may be repeated once after a period of from ten days to two weeks.

**NOTE.**—Broken capsules should be discarded; the solution should never be employed if it has been exposed to the air for more than a very brief time, because of the possibility of phosphine formation by decomposition.

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## CHAPTER VI

# Antispasmodic Preparations

Antispasmodic preparations include those agents that are used to relax either smooth or skeletal muscle. This chapter accordingly includes both curare and papaverine preparations. Most agents that are ordinarily classified as antispasmodics act on smooth muscle. Because many of these produce effects commonly or primarily associated with functions of the vegetative nervous system, they are described in the chapter on Autonomic Drugs. Nitrite and organic nitrates that act against vascular spasm are described in the chapter on Cardiovascular Agents.

Curare has long been a useful pharmacologic agent for laboratory investigation but it has only recently come into general use as a therapeutic agent. The crude drug is an extract obtained from certain species of *Strychnos* and *Menispermaceous* plants that are employed by South American Indians as an arrow poison. Commercial extracts were formerly imported in three forms that were designated according to the container in which they were shipped: tubocurare, in bamboo tubes; calabash curare (from *Strychnos toxifera*), in gourds; pot curare, in earthenware jars. The active principles of curare are alkaloids that differ in each variety of the crude extract. Crude curare contains a large number of alkaloids: of these *d*-tubocurarine and toxiferin have been obtained in a pure state and are quaternary bases. Curine which occurs in many varieties of curare effects chiefly the nervous system. Calabash curare frequently contains toxiferin, an extremely potent alkaloid, its pharmacology has not as yet been fully determined. The exact chemical structure of all curare alkaloids has not been completely elucidated. The curare alkaloids obtained from *Chondodendron tomentosum* and closely related species of the moon seed family are for the most part bisbenzylisoquinoline compounds containing oxygen in both phenolic and ether linkages. There does not appear to be a close relationship between curariform activity and chemical structure, however, many quaternary ammonium compounds have a curare-like action. Curare blocks synaptic transmission of the autonomic nervous system and blocks neuromyic transmission to skeletal muscle. It can thus be considered chiefly as an antispasmodic of skeletal muscle, the tone or contractile power of which is reduced by the specific peripheral effect of the drug. Therapeutic doses produce the following sequence of skeletal muscle depression: ptosis, imbalance of the extra-ocular muscles with inability to raise the head, and partial relaxation or complete paralysis of the long muscles of the back and the muscles of the

extremities. With larger doses, the last structures to be affected are the intercostal muscles and finally, the diaphragm. As these muscles become curarized, respiration becomes shallow and may cease. This sequence follows the order of involvement frequently encountered in myasthenia gravis. Paralysis recedes in reverse order after the full effect is manifest, the extent and duration of action being dependent on the size of the dose. Recovery may require 15 to 20 minutes following a single dose.

Curare paralyzes skeletal muscle before ganglionic action is fully developed; the paralysis also usually masks the stimulant and convulsant action of the drug on the central nervous system. The blocking action of curare on skeletal muscle is somewhat analogous to that of atropine on certain smooth muscle. Curare blocks the "nicotinic" actions of acetylcholine and it differs from nicotine in the much less pronounced effect on ganglia, the lack of initial stimulatory action, and inability specifically to stimulate respiration. Both physostigmine and neostigmine are pharmacologic antagonists to curare.

Curare preparations for therapeutic use have been developed in partially purified form and in the purer form of its chief alkaloid principle, dextrorotatory tubocurarine. Until more is known of the exact chemical structure of curare alkaloids, curare preparations should be bioassayed for curare potency, although the crystalline chloride salt of *d*-tubocurarine may be prescribed on a weight basis. Curare potency is presently measured by bioassay in rabbits and is adjusted to a standard head drop dose of *d*-tubocurarine chloride that falls within the range of 0.125 to 0.175 mg./Kg. A provisional unit (about one-tenth of the standard head drop dose) has also been designated as the equivalent in physiologic activity of 0.15 mg. of *d*-tubocurarine chloride in rabbits (2 Kg.). Curare should be employed only by those thoroughly familiar with its dosage, effects and dangers. Solution of neostigmine methylsulfate, 1:2000 should always be on hand for injection to combat respiratory failure during the use of curare.

**PURIFIED CHONDODENDRON TOMENTOSUM EXTRACT—Intocostrin-Squibb.**—A preparation containing therapeutically effective constituents of raw (crude) curare. The curare activity is due almost wholly to the presence of an alkaloid, *d*-tubocurarine, which accounts for about half the total solids in Intocostrin exclusive of added sodium chloride and chlorobutanol. The physiologic activity of Intocostrin is determined on rabbits. The provisional unit is a potency equivalent to that of 0.15 mg. of *d*-tubocurarine chloride pentahydrate.

For tests and standards, see Section B.

**Actions and Uses.**—Intocostrin is used for the same purposes as its chief active principle, *d*-tubocurarine. See the monograph, *d*-Tubocurarine Chloride.

**Dosage.**—In diminishing the convulsions of shock therapy or to produce relaxation in manipulative procedures: one unit per

kilogram of body weight (but the initial dose for adults should be 20 units less than this total), administered intravenously at a uniform rate during one to one and one-half minutes. Larger doses may be necessary, but if the estimated dose fails to produce paralysis another full paralyzing dose should not be given for twenty-four hours. Everything required to cope with respiratory failure should be at hand at all times. Neostigmine methylsulfate solution, 1:2,000, should be at hand for intravenous injection if required, and an airflow should be available on the tray to assist in artificial respiration in the event of obstructed breathing. In spastic and athetoid states in children: 0.5 to 1.5 units per pound of body weight administered intramuscularly at four day intervals. As a diagnostic agent in myasthenia gravis: one fifteenth to one fifth of the average adult dose intravenously, followed always in two or three minutes by the intravenous injection of 1.5 mg. of neostigmine methylsulfate with 0.65 mg. of atropine sulfate.

In order to obtain muscular relaxation during light (second plane) anesthesia with cyclopropane, nitrous oxide or barbiturates, 40 to 60 units of purified chondrodendron tomentosum extract may be administered when the skin incision is made: 20 to 30 units may be added in three to five minutes, if needed. If the operation has lasted more than forty-five minutes, an additional dose of 30 to 40 units may be cautiously administered if such additional dosage seems indicated. In an alternative method as much as 100 units has been administered in a single intravenous injection at the beginning of or during anesthesia, but no additional quantities should be given following this large dose until some time has elapsed and then extreme caution exercised. The drug apparently may be used with any type of anesthetic agent, *although with ether only about one-third of the dose otherwise employed should be used.* It must be remembered, however, that the use of purified chondrodendron tomentosum extract as an adjuvant to surgical anesthesia is still in a stage which requires continued careful study.

Curare has been extensively used with sodium pentothal anesthesia, usually by separate injection. If a barbiturate solution (alkaline) is mixed with Intocostarin solution (acid) a precipitate is formed, which is redissolved when a sufficient amount of the barbiturate with its buffer has been added. The precipitate is the free barbituric acid derivative. If an Intocostarin solution is alkalized with sodium carbonate, no loss in potency occurs during a twenty-four hour period and no precipitate forms when the alkalized solution is mixed in any quantity with a barbiturate solution. Such mixtures have not been used clinically; the present method is to inject the solution separately and alternately through a Y-tube using the same needle. When by this method Intocostarin follows the barbiturate, a slight fine precipitate forms at the surface of contact of the two solutions. It has been the custom to allow such a precipitate to be injected slowly, as it presumably redissolves on mixing with the plasma.

**Preparation.**—

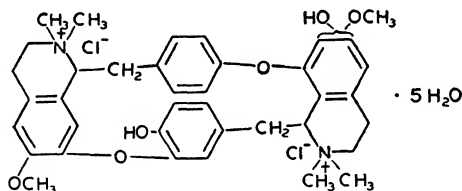
Intocostrin prepared from *Chondodendron tomentosum* extract is made by first extracting with alcohol a desiccated curare obtained from a heavy syrup of the bark and stems of *Chondodendron tomentosum*. The alcoholic extract is evaporated to dryness; a sterile filtered solution having a pH of 4.6-4.8 is made and adjusted to a standard potency of 20 units per cubic centimeter. The final solution contains sodium chloride 0.45 per cent and trichlorobutanol 0.5 per cent; sterilized by filtration and its pH again adjusted to 4.6-4.8.

E. R. SQUIBB & SONS

**Intocostrin:** 5 cc. and 10 cc. vials. Each cubic centimeter contains an amount of Intocostrin equivalent to 20 units: sodium chloride 0.45 per cent and chlorobutanol 0.5 per cent as a preservative.

U. S. trademark 382,110.

***d*-TUBOCURARINE CHLORIDE.**—The crystalline chloride of a quaternary base alkaloid obtainable from the bark and stems of *Chondodendron tomentosum* and related species.—*d*-Tubocurarine chloride is standardized biologically by the rabbit "head-drop" method. The standard "head-drop" dose HD<sub>50</sub>, calculated as *d*-tubocurarine chloride pentahydrate, is 0.15 mg. per kilogram of body weight. The structural formula of *d*-tubocurarine chloride may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—*d*-Tubocurarine chloride may be used in conditions in which it is desirable to reduce the tone or contractile power of skeletal muscle. It is useful with light general anesthesia to obtain greater relaxation of the musculature in abdominal surgery and orthopedic manipulative procedures, to diminish the violence of muscular contractions during metrazol or electric shock therapy, and temporarily to lessen spasticity due to injury of the central nervous system or in certain spastic states of neurologic origin. It may also be used as a diagnostic agent in cases suspected to be affected with myasthenia gravis.

**Dosage.**—In conjunction with light surgical or orthopedic anesthesia, premedication should be carried out as usual. The following doses are applicable with general anesthetics *except ether*, when only one-third of the recommended dose should be employed. The patient is maintained at light surgical anesthesia until the stage of the operation is reached at which the greatest



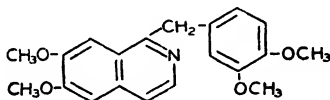
muscular relaxation is required. At that time 6 to 15 mg. may be given as a single intravenous injection. This is sometimes effective in about two minutes; if respiration ceases, the anesthetist must be prepared to continue the pulmonary exchange by pressure on the bag of the anesthetic apparatus. The dose may be calculated on the basis of 1 mg. for each 10 lb. of body weight (*one-third this amount when ether is the anesthetic*).

In therapeutic shock treatment, the usual dose is 3 mg. for each 40 lbs of body weight; for greater safety 3 mg. less than the calculated amount should be used as the initial dose and the intravenous injection should always be given over a period of not less than 90 seconds. In spastic states, where the drug is used to permit training in the voluntary use of muscles, it may be administered intramuscularly at four day intervals. The dose is determined by trial, beginning with 3 mg. for each 40 lbs. of body weight and gradually increasing the dose until the amount producing best results is found. As a diagnostic test for myasthenia gravis, 0.3 mg. per 40 lbs. of body weight is given intravenously; marked exaggeration of symptoms appears within two minutes. As soon as a positive reaction is confirmed, the curare effect should be antagonized immediately by the intravenous injection of 1 cc. of neostigmine methylsulfate, 1:2,000 combined with 0.6 mg. of atropine sulfate. The former drug should always be on hand to combat respiratory failure during the use of curare.

Solutions of *d*-tubocurarine chloride used in conjunction with pentothal sodium intravenous anesthesia may be admixed with a solution of pentothal sodium for simultaneous administration of both agents. Solutions of *d*-tubocurarine chloride are available in concentrations of 3 mg. (20 units) per cubic centimeter and 15 mg. (100 units) per cubic centimeter. The acidity of these solutions causes only momentary precipitation of curarebarbiturate mixtures when added in amounts to avoid undue dilution of the pentothal sodium solution: limit for solution *d*-tubocurarine of 3 mg. (20 units) per cc., is 7.5 units per 25 mg. pentothal sodium in 1 cc.; for solution *d*-tubocurarine of 15 mg. (100 units) per cc., 10 units per 25 mg. pentothal sodium in 1 cc. Optimal results for most operative procedures have been obtained by using 5 units of the higher potency *d*-tubocurarine solution per each 1 cc. of the 2.5 per cent solution of pentothal sodium. This mixture is made up by adding 1 cc. of high potency (100 units per cc.) solution of *d*-tubocurarine chloride to 19 cc. of 2.5 per cent solution of pentothal sodium and when so made from the high potency *d*-tubocurarine chloride solution will keep for about 10 days. It is administered in the same manner as pentothal sodium alone, with slow induction, 1 or 2 cc. at a time. The average total dose of the mixture varies from 15 to 20 cc. Other ratios and technics may be worked out to advantage in individual cases. *The high potency solution of d-tubocurarine chloride, 15 mg. (100 units) per cc. should never be injected without dilution because of the danger of overdosage by too rapid administration. d-tubocurarine chloride-barbiturate*

combination anesthesia is contraindicated in patients with respiratory deficiencies, pulmonary disorders, renal dysfunction, liver disease and myasthenia gravis.

**PAPAVERINE.**—An alkaloid obtained from opium, belonging to the benzyl isoquinoline group (that is, it is not a morphine derivative). The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Pal found that papaverine relaxes smooth muscle in general, although different organs are affected in a varying degree.

Papaverine is most effective in hypertonic conditions, while it does not interfere materially with the normal movements, for instance, of the intestines. It is also a rather feeble central analgesic and a local anesthetic. Its toxicity is low, and neither tolerance nor habituation has been reported. These actions have prompted its use, with reported success, in various spasmodic conditions of the smooth muscles. Pal recommends it especially in all kinds of gastric and intestinal spasms (also for the diagnosis of pyloric spasm), in biliary colic, and in bronchial spasm. However, it has never come into wide use for these purposes. Of even more doubtful value is its employment in pertussis, hyperemesis, and vascular spasm—angina pectoris, acute uremia and eclampsia. It may be useful intravenously against reflex vascular spasm to increase collateral circulation in peripheral arterial embolism. It is ineffective in chronic hypertension.

**Dosage.**—The oral and hypodermic single dose is from 30 mg. to 80 mg.; daily dose to 0.5 Gm. Single doses of even 1 Gm. are said to be nontoxic.

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## CHAPTER VII

# Astringents, Caustics and Sclerosing Agents

Astringents are agents used locally for their relatively weak precipitant action on proteins. Tannic acid is the most important of the vegetable astringents. Many metallic salts possess astringent action, notably salts of zinc, lead, copper and aluminum. The salts of other metals such as silver and mercury, used primarily for their germicidal effect, are astringent in high dilutions. These are described in the chapter on Local Anti-Infectives. Aluminum compounds used as antacids are described in the chapter on Gastrointestinal Drugs.

Caustics are agents used locally for chemical cautery or destruction of tissue. The mineral acids and strong alkalis are perhaps the best examples. Of greater therapeutic usefulness, are certain metallic compounds such as silver nitrate and copper sulfate that are astringent in high dilutions, but act as caustics in concentrated form. The term escharotic, though synonymous with caustic, is occasionally applied to agents that produce local protein-coagulant effects rather than complete destruction of tissue.

Sclerosing agents are described in this chapter because of their irritant properties, which make them useful for the obliteration of varicose veins. The Council has not accepted agents of this type for other purposes; their use in the treatment of hernia is considered hazardous.

## Aluminum Salts

Several of the compounds of aluminum are official, including the ordinary alum or alumen, U. S. P. Aluminum acetate and aluminum subacetate are used in the form of solutions and are described in The National Formulary as Aluminum Acetate Solution and Aluminum Subacetate Solution.

The aluminum compounds are used for their astringent action. Since they are but little absorbed, they are relatively nontoxic.

Compounds of aluminum are astringent because of their property of precipitating albumin. The exsiccated alum is more energetic, not only because it contains a larger proportion of alum than the crystalline form, but because it absorbs water from the tissue at the same time. The acetate is milder than the sulfate, as is usual with metallic salts.

The aluminum compounds are not so astringent as the corresponding lead salts, but they may exert an irritant and even caustic action when used in concentrated solutions or in the form of the exsiccated (burnt) alum. When swallowed in overdoses in such concentrated form, they may cause gastritis and diarrhea. Alum is sometimes used as an emetic.

The aluminum compounds are slightly antiseptic, a property which goes with their astringency. Some of the organic compounds are said to be more actively antiseptic than the inorganic ones.

Several proprietary preparations, consisting of aluminum combined with organic acids, have been introduced with a view to utilizing the astringent and antiseptic properties of their components. Many of these possess no special advantages and have fallen into disuse, or have been largely replaced by others of a more or less similar nature.

### Copper Salts

**CUPRIC CITRATE-U. S. P.**—"The cupric salt of citric acid and contains not less than 34 per cent and not more than 37 per cent of Cu. [copper]." *U. S. P.*

For description and standards see the U. S. Pharmacopeia under Cupric Citrate and Cupric Citrate Ointment.

*Actions, Uses and Dosage.*—Copper citrate possesses the astringent and antiseptic properties of other salts of copper, somewhat modified by its sparing solubility.

It may be used for the same purposes as, and in doses similar to, those of other salts of copper. Ointments of 5 to 10 per cent are used locally for the treatment of trachoma.

MALLINCKRODT CHEMICAL WORKS

Copper Citrate (*Crystals*): bulk.

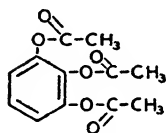
MANHATTAN EYE SALVE COMPANY, INC.

**Ophthalmic Ointment Copper Citrate 5 per Cent:** A sterile ointment containing copper citrate 5 per cent, wool fat 10 per cent, petrolatum 85 per cent, without alcohol or preservative.

**Ophthalmic Ointment Copper Citrate 10 per Cent:** A sterile ointment containing copper citrate 10 per cent, wool fat 10 per cent, petrolatum, 80 per cent, without alcohol or preservative.

### Pyrogallol

**ACETPYROGALL**—Lenigallol.-Bilhuber-Knoll.—Triacetyl pyrogallol.—Obtained by replacing the hydroxyl groups of pyrogallol with acetate groups. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Acetpyrogallol as such is said to be non-poisonous and nonirritating, but it produces a mild and painless corrosive effect by the gradual liberation of pyrogallol.

It is used as a substitute for pyrogallol in psoriasis, lupus, acute and subacute eczema of children and other skin diseases.

**Dosage.**—In 5 to 10 per cent ointment, usually with zinc oxide.

BILHUBER-KNOLL CORP.

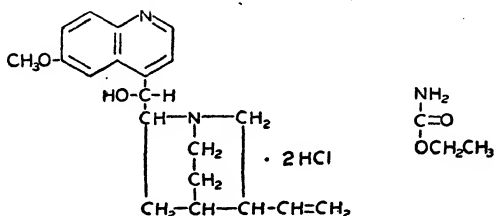
**Lenigallol-Zinc Ointment:** Contains lenigallol 6 per cent, in zinc oxide ointment-U. S. P.

**Lenigallol (Powder):** 7.5 Gm. and 30 Gm. bottles.

### Sclerosing Agents

Solutions of ethyl alcohol, dextrose, invert sugar, iodides, iron salts, mercuric chloride, phenol, quinine and urea hydrochloride, salicylates, sodium chloride, sodium citrate, sodium morrhuate and others have been employed as sclerosing agents mainly for the obliteration of varicose veins. Some of the compounds employed for this purpose are combined with local anesthetic agents or possess anesthetic properties themselves. Solutions of dextrose or invert sugar and fatty acid preparations such as sodium morrhuate are less irritating and do not produce necrosis if accidentally injected outside the vein as may occur with more powerful sclerosing substances. The Council has recognized solutions of dextrose (50 per cent), dextrose (25 per cent) and sodium chloride (15 per cent) combined, invert sugar (60 to 75 per cent), sodium morrhuate (5 per cent) combined with local anesthetics, quinine hydrochloride or dihydrochloride (13 per cent) with urethane (6.5 per cent), and sodium ricinoleate solution for use as sclerosing agents in the obliteration of varicose veins only. Sclerosing therapy of varicose veins is contraindicated in the presence of incompetency of the collateral deep veins of the lower extremities and before ligation of the greater saphenous vein in the presence of incompetency of the valves of that vein; other contraindications include active or recent phlebitis, systemic diseases such as active tuberculosis and hyperthyroidism, acute infections (including the common cold), prolonged recumbency, cardiac decompensation and possibly, pregnancy. In the occasional case where a patchy dermatitis appears, usually of the legs, and recurs or is exaggerated following succeeding injections of a sclerosing agent it is well to discontinue the use of such agents.

**QUININE DIHYDROCHLORIDE AND URETHANE.**—A sterile aqueous solution containing quinine dihydrochloride U. S. P. 12.7 Gm. and urethane U. S. P. 6.65 Gm. in each hundred cubic centimeters. The structural formulas of these compounds may be represented, respectively, as follows:



For standards see U. S. Pharmacopeia under Quinine Dihydrochloride and under Urethane.

**Actions and Uses.**—A mixture of quinine dihydrochloride and urethane in aqueous solution is used as a sclerosing agent for injection in the obliterative treatment of varicose veins. The mixture is claimed to have antiseptic qualities. It should not be employed during menstruation, pregnancy nor in the presence of heart disease, nephritis, diabetes, upper respiratory infection or septic tonsillitis. It is contraindicated in the presence of phlebitis, suppurative ulceration and incompetence of deep veins.

**Dosage.**—The initial injection should be limited to 0.5 cc. to determine whether idiosyncrasy exists; average amount for injection at any one site is 1 cc. and should not exceed 2 cc. The total quantity to be injected at a single sitting should not exceed 5 cc. to avoid the production of cinchonism. The injection should be made slowly to avoid dangerous consequences.

**DEXTROSE SOLUTION 50%.**—See monograph on Invert Sugar Solution for actions and uses.

**INVERT SUGAR SOLUTION.**—A solution of a mixture of dextrose and levulose obtained by the inversion of sucrose.

For tests and standards, see Section B.

**Actions and Uses.**—Solution of invert sugar is used in the injection treatment of varicose veins. It is claimed that the use of sugar solutions such as solutions of dextrose or of invert sugar have the advantage over solutions of sodium chloride, sodium salicylate or mercuric chloride in that they do not cause severe cramps or sloughing if accidentally injected outside the vein.

**Dosage.**—Depending on the size of the vein, from 5 to 20 cc. of solution is injected. For young patients whose veins react to solutions of lower concentration, solutions containing from 50 to 60 Gm. of invert sugar in 100 cc. are used; for older

patients and varicosities of long standing, a solution containing 75 Gm. of invert sugar in 100 cc. is used.

**SODIUM MORRHUATE INJECTION-U. S. P.**—"A sterile solution of the sodium salts of the fatty acids of cod liver oil. It contains, when determined by the [U. S. P.] assay method . . . not less than 93 per cent and not more than 107 per cent of the labeled amount of sodium morrhuate. A suitable preservative, not to exceed 0.5 per cent, and ethyl or benzyl alcohol, not to exceed 3 per cent, may be added." *U. S. P.*

For standards see the *U. S. Pharmacopeia* under Sodium Morrhuate Injection.

*Actions and Uses.*—The action of sodium morrhuate is that of a sclerosing agent. It is employed in solution with addition of a local anesthetic for the obliteration of varicose veins. Solutions in concentrations of more than 5 per cent are not recommended, and the possibility of sensitization or idiosyncrasy to sodium morrhuate should be kept in mind to avoid reactions which have been reported in susceptible individuals.

*Dosage.*—0.5 to 1 cc. of a 5 per cent solution is a relatively safe preliminary test dose and its effects should be studied for 24 hours before proceeding with further injections. An average of 1 cc. is the amount injected at any one site and should not exceed 2 cc. Injection of the saphenous vein at the time of ligation when that procedure is indicated, may require from 5 to 10 cc. of the 5 per cent solution. The number of injections made in one day varies with the patient and should not comprise a total amount of more than 5 cc. To guard against the development of sensitivity it is recommended that the interval of time between the first two injections be not more than five days.

GEORGE A. BREON & COMPANY, INC.

**Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%:** 5 cc. vials. Each cubic centimeter contains sodium morrhuate 50 mg. and benzyl alcohol 20 mg. in aqueous solution.

BURROUGHS WELLCOME & Co., INC.

**Solution Sodium Morrhuate Injection 5%:** 25 cc. rubber-capped bottles. Each cubic centimeter contains sodium morrhuate 50 mg. and 0.5 per cent of phenol as a preservative.

ENDO PRODUCTS, INC.

**Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%:** 2 cc. and 5 cc. ampuls and 25 cc. bottle. Each cubic centimeter contains sodium morrhuate 50 mg.; and benzyl alcohol 20 mg. in aqueous solution.

LAKESIDE LABORATORIES, INC.

**Solution Sodium Morrhuate 5% and Benzyl Alcohol 2%:** 5 cc. and 30 cc. vials. Each cubic centimeter contains 0.05 Gm. of sodium morrhuate and 0.02 Gm. of benzyl alcohol in aqueous solution.

NATIONAL DRUG COMPANY

**Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%:** 5 cc. ampuls and 25 cc. ampul-vials. Each cubic centimeter contains 50 mg. sodium morrhuate and 20 mg. benzyl alcohol in aqueous solution.

G. D. SEARLE & Co.

**Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%:** 5 cc. and 60 cc. (serum-type ampuls). Each cubic centimeter contains 50 mg. sodium morrhuate and benzyl alcohol 20 mg. in aqueous solution.

ULMER PHARMACAL COMPANY

**Solution Sodium Morrhuate 5% with Benzyl Alcohol 3%:** 5 cc. and 20 cc. vials. Each cubic centimeter contains sodium morrhuate 50 mg., benzyl alcohol 30 mg. and phenol 5 mg., in aqueous solution.

THE UPJOHN COMPANY

**Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%:** 2 cc. ampuls and 30 cc. vials. Each cubic centimeter contains sodium morrhuate 50 mg. and benzyl alcohol 20 mg. in aqueous solution.

**SODIUM RICINOLEATE SOLUTION.** — Soricin Sclerosing Solution, 2%-Merrell.—A sterile, aqueous solution containing 2 Gm. of purified sodium ricinoleate per 100 cc. Sodium ricinoleate has the following structural formula:



For tests and standards, see Section B.

*Actions and Uses.*—Sodium ricinoleate, like other fatty acid salts is irritant to tissues, and in solution it exerts a useful sclerosing action for the obliteration of varicose veins by injection. Following injection into a varicosity, there is immediate fragmentation of the red blood cells and formation of a jelly-like clot, which resists resolution or absorption for a long period of time. Because of the irritation and destruction of the intima, the thrombus adheres to the wall of the vein. Subsequently there is fibrosis of the vein. Recanalization seldom occurs.

As with other sclerosing solutions, sodium ricinoleate solution is contraindicated for injection of varicose veins in obstruc-



tion of the deep (collateral) circulation, phlebitis, infected varicose ulceration, uncontrolled diabetes, arteriosclerosis and hypertension. Sensitivity or allergic reaction to sodium ricinoleate solutions may occasionally be encountered, so it is essential to begin treatment with a preliminary test dose as indicated in the following paragraph.

*Dosage.*—Sodium ricinoleate for injection of varicose veins is usually employed as a 2 per cent solution. This is considered the concentration of choice for all but the smallest lesions. Small telangiectasia may be injected intradermally with a 0.5 per cent solution, agitated to produce a frothy mixture with air that avoids undue hemolysis and subsequent brown pigmentation of the skin. Superficial venous ruptures (bursts or flares) may be treated with an injection of 0.25 to 0.5 per cent concentrations into the most central of the veins involved.

The quantity to be injected depends on the size of the vein and the amount of blood stasis: 2 to 5 cc. of the 2 per cent solution is usually sufficient for injection of the trunk of the great saphenous vein when ligation of that structure is indicated. The average dose of the 2 per cent solution for localized varicosities ranges from 1 to 2 cc., and not more than 10 cc. is recommended for injection of various sites at one time of administration. Treatments may be repeated at intervals of one week. The smallest lesions usually require not more than 0.25 to 0.5 cc. of the drug in the lower concentrations. Care must be taken to avoid extravascular injection of the 2 per cent solution because of danger of sloughing of tissue.

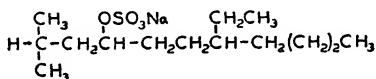
All patients should be tested for possible sensitivity to sodium ricinoleate by injection of 0.5 cc. of the 2 per cent solution into a small varicosity four or five days before actual treatment is started. In patients who show a reaction to the test dose, the drug should not be used.

THE WM. S. MERRELL CO.

**Solution Soricin Sclerosing 2% :** 20 cc. vials. Each 100 cc. contains 2 Gm. of sodium ricinoleate.

U. S. patent 1,936,456. U. S. trademark 244,397.

**SODIUM TETRADECYL SULFATE.** — Sodium-2-methyl-7-ethylundecyl sulfate-4.—The structural formula of sodium tetradecyl sulfate may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Sodium tetradecyl sulfate is an anionic surface active agent that has been found to be useful as a wetting agent to increase the surface activity of solutions of certain ex-

ternally applied antiseptics to which it may be added. It also possesses sclerosing properties useful for the obliteration of varicose veins by intravascular injection of buffered solutions in appropriate concentration. Its rather profound sclerosing action is subject to the disadvantage that injections outside of the vein may produce sloughing and that injection into the vein may more frequently be associated with pain especially in the higher dose range. On the other hand the possibilities of sensitization are considered remote and idiosyncrasies or anaphylactoid reactions that have rarely occurred are mild and of short duration. The possibility of undiscovered toxic effects should be borne in mind, but careful clinical studies to date appear to warrant use of the compound as a reasonably safe sclerosing agent.

Sodium tetradecyl sulfate is subject to the same general contraindications as for other sclerosing agents. See general statement on Sclerosing Agents.

*Dosage.*—Sodium tetradecyl sulfate is employed for sclerosing therapy of varicose veins in buffered solutions of 1 per cent, 3 per cent and 5 per cent concentrations depending on the size of the veins (amount of hemodilution) to be obliterated. The 3 per cent is considered adequate for most sites. The average amount to be injected at any one site should be from 0.5 cc. to 1.0 cc. and at any one sitting, 2 cc. to 3 cc. Not more than 6 cc. of the 5 per cent solution or 10 cc. of the 3 per cent solution should be injected at any one occasion. Repeated injections should be carried out at weekly intervals. The 1 per cent concentration should be used for all small superficial varicosities to avoid possible sloughing that may occur with the use of stronger concentrations for such veins. It is further recommended that not more than 1 cc. of the 1 per cent concentration be used as a test dose on the first injection to detect any possible idiosyncrasy. Treatment should not be instituted or continued if alarming reactions occur.

WALLACE & TIERNAN PRODUCTS, INC.

**Solution Sodium Sotradecol with Benzyl Alcohol 2% :**  
1, 3 and 5 per cent solution, 20 cc. vials.

U. S. trademark registered.

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## CHAPTER VIII

# Autonomic Drugs

The designation "autonomic drugs" is generally applied to those drugs that either mimic or oppose the peripheral effects of nerve impulses of the autonomic (visceral efferent, vegetative, involuntary) nervous system. They have been grouped into four main classes of drugs on the bases of (a) the two anatomical divisions of the autonomic system, namely the sympathetic (thoracolumbar) and the parasympathetic (craniosacral), and (b) the two principal effects, whether stimulating or depressing, upon the given division. Accordingly, the four classes are (1) sympathomimetic, (2) sympatholytic, (3) parasympathomimetic, and (4) parasympatholytic. Since the two divisions are, on the whole, mutually antagonistic, it is seen that drugs of classes (1) and (4) have certain effects in common; thus atropine, which is parasympatholytic, and epinephrine, which is sympathomimetic, both dilate the pupil. Similarly (2) and (3) will sometimes have identical effects.

Certain discrepancies, however, are found in the effects produced by members of these groups and between members of the same group. These discrepancies are partially explained by the known facts of chemical mediation of the nervous impulse. Autonomic fibers that transmit nerve impulses mediated by the epinephrine-like substance or substances called sympathin are called *adrenergic*; most postganglionic sympathetic fibers are of this sort. Autonomic fibers that carry nerve impulses mediated by acetylcholine are called *cholinergic*; all postganglionic parasympathetic fibers, as well as all preganglionic fibers of both sympathetic and parasympathetic divisions are of this sort. Acetylcholine has also been associated with the mediation of impulses by "sympathetic" nerves to sweat glands and certain vascular beds, the splanchnic fibers to the adrenal medulla, and even the cerebrospinal motor fibers to skeletal muscle.

The uncertainty that prevails regarding the exact mode and site of action of so-called autonomic drugs makes it difficult to adopt a scheme of classification that takes into account all of their variable effects. One advantage in partially retaining an anatomical viewpoint is that fibers of the sympathetic branch ramify widely through several ganglionic cells so that a diffuse discharge is possible, whereas parasympathetic fibers have terminal ganglia near to the innervated organ so that impulses are more discrete in their effect. Furthermore, cholinesterase causes a rapid destruction of acetylcholine thereby limiting the effect of cholinergic nerves, whereas sympathin and epinephrine disappear less rapidly and may thus be carried in the blood stream

to produce the widespread effects of generalized adrenergic stimulation. It may also be significant that no gland is known to exist in the body for the elaboration of acetylcholine as for epinephrine.

### Sympathomimetic Agents

Sympathomimetic agents are broadly defined as those drugs that induce bodily responses which imitate the effects of impulses conveyed by adrenergic postganglionic fibers of the sympathetic nervous system. Most of these agents are aromatic compounds, and their similarity of action is explained by a similarity of chemical structure in that the benzene nucleus which constitutes the aromatic portion of the molecule is separated from an amino nitrogen atom by two carbon atoms of the aliphatic portion of the molecule. Certain capabilities for substitution in either the aromatic or aliphatic portions have led to the synthesis of a large number of sympathomimetic amines, which, although retaining sympathomimetic activity, exhibit new properties that have useful clinical application. Chemically dissimilar compounds that possess sympathomimetic activity have also been developed.

Because of the existing similarities of structure, sympathomimetic agents can be grouped, sometimes according to their aromatic portions, sometimes according to the aliphatic. Thus, epinephrine and Kephrene have identical aromatic portions; ephedrine and Propadrine are similarly paired; so are tyramine and Paredrine. Again, epinephrine and phenylephrine have identical aliphatic portions; amphetamine and Paredrine are similarly paired. Amphetamine, Paredrine, and Tuamine possess, as a common feature, an aliphatic 3-carbon chain with an amino group attached to the middle carbon atom; their differences must lie in the rest of the molecule. Amphetamine is distinguished by a simple benzene ring, while Paredrine has a benzene ring with one OH-group added; in place of the benzene ring, Tuamine has a butyl group. As in the case of certain other drugs, it is generally true for sympathomimetic agents that when stereoisomeric forms exist the dextrorotatory form may differ greatly in activity from the levorotatory form.

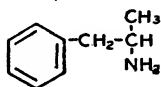
Ephedrine, amphetamine, and phenylephrine differ in action from epinephrine in that their excitatory actions are only diminished, and not reversed, by the sympatholytic agents (egotoxine, dihydroergotamine, Dibenamine, Priscol), and cocaine (possessing certain sympathomimetic properties) does not potentiate their effects. Most of the pharmacologic differences between ephedrine and epinephrine are well known, but may be repeated to illustrate those that may exist between other members of this class of autonomic drugs. Ephedrine in contrast to epinephrine is effective orally, has more prolonged action, produces less marked arteriolar constrictor effect, fails to exert its characteristic activity if given too frequently (tachyphylaxis) and produces effects on skeletal muscle not shared by epinephrine. The central stimulatory effects of ephedrine and amphetamine put these

compounds at a disadvantage when their peripheral effects are desired, but at the same time render them useful under other circumstances.

With cognizance of certain exceptions, sympathomimetic drugs in general produce mydriasis and/or relaxation of the ciliary muscle, decreased tone of bronchioles, stomach, intestine, bladder and ureter, contraction of smooth muscle sphincters, the splenic capsule, and pregnant uterus, constriction of blood vessels other than coronary, inhibition of the secretion of certain glands and increased cardiac rate and output. The actions on the heart, blood vessels and certain smooth muscles are especially prominent and form the basis for their principal therapeutic application. Ventricular arrhythmias, even fibrillation, may follow the use of epinephrine, particularly during surgical anesthesia, so that its use may be dangerous in such circumstances. In patients with medical or surgical shock, it may aggravate the underlying cause; it should not be given in the presence of emphysematous bronchial asthma. Pressor effects of any of these compounds are to be avoided in hyperthyroidism and hypertensive heart disease. The cardiovascular response to a sympathomimetic amine is frequently modified by the presence of a previous dose of the same, or another amine. The pressor response may be increased or decreased, and in some instances inverted to a depressor action. For instance, Vonedrine pressor action is inverted to a depressor action by the presence of Paredrine, but not by other amines. Epinephrine, while the most potent pressor amine, produces a dilator effect on capillaries that may account for the hypotension seen to follow its transient vasoconstrictor action on the arterioles. Reversal of its constrictor action occurs when preceded by the sympatholytic agents.

Milder side reactions of anxiety, tenseness, restlessness, insomnia, tremor, weakness, palpitation may also interfere with the clinical use of these compounds in certain patients. The claimed advantage of one compound over another in this group is largely dependent upon the purpose for which it is employed, so that what may be considered an undesirable side effect in one instance, becomes a useful therapeutic action in another.

**AMPHETAMINE**—**Benzedrine**—Smith, Kline & French.  
—Racemic Amphetamine.—1-Phenyl-2-aminopropane.—Racemic desoxy-nor-ephedrine.—A synthetically prepared racemic mixture having the formula:



For tests and standards, see Section B.

**Actions and Uses.**—Amphetamine produces local effects similar to those of ephedrine. Inhalation of the vapors of amphetamine or its carbonate produces shrinking of the nasal mucosa

in head colds, sinusitis, vasomotor rhinitis, hay fever and asthma. Both amphetamine and its carbonate (the latter readily forms on exposure of amphetamine to air) are volatile. Its use is contraindicated in those who suffer from cardiovascular disease and in those who show either sensitivity or pressor effect from its use in therapeutic doses.

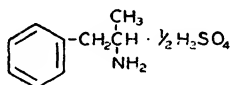
*Dosage.*—As an inhalant, one or two inhalations through each nostril at hourly intervals, has been recommended. Continued overdosage should be guarded against, as this has caused restlessness and sleeplessness and also may prolong the local condition being treated. Serious reaction has been reported as a result of overdosage and what may be hypersensitivity to the drug in inhalator form.

SMITH, KLINE & FRENCH LABORATORIES

**Benzedrine Inhaler:** Each inhaler tube contains, at the time of packing racemic amphetamine 250 mg., menthol 12.5 mg. and aromatics.

U. S. patents 1,921,424 (Aug. 8, 1933; expires 1950), 1,879,003 (Sept. 27, 1932; expires 1949) and 2,015,408 (Sept. 24, 1935; expires 1952). U. S. trademarks 272,377 and 330,017.

**AMPHETAMINE SULFATE.**—**Benzedrine Sulfate.**—Smith, Kline & French.—Racemic Amphetamine Sulfate.—Racemic desoxy-nor-ephedrine sulfate.—1-Phenyl-2-amino-propane sulfate. The structural formula of this compound may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Amphetamine sulfate has a number of clinical uses. It has been widely employed in the treatment of narcolepsy; in controlling the oculogyric crises and various other manifestations of postencephalitic parkinsonism; as an adjunct in the treatment of alcoholism; and for facilitating roentgenographic studies of the gastrointestinal tract; but its most extensive therapeutic application has been in the treatment of certain depressive conditions, especially those characterized by apathy and psychomotor retardation.

The marked central nervous stimulatory effect of the drug on the central nervous system renders it effective in the symptomatic treatment of many mild psychogenic depressive states, especially those marked by morning tiredness, attending old age, accompanying persistent pain, precipitated by the menopause, characterized by chronic fatigue, masquerading as bodily ailments, following childbirth, prolonged postoperative recovery, associated with chronic organic disease, etc.

Amphetamine sulfate may also be of value, but to a lesser

extent, in the symptomatic treatment of the more severe depressions accompanying certain major psychopathic conditions.

There is considerable evidence that, again due to its ameliorative influence on mental depression, amphetamine is useful as an adjunct in the treatment of alcoholism. In chronic alcoholism, especially, it may provide a desirable means of interrupting the vicious alcoholic cycle, thus permitting the institution of more fundamental psychotherapeutic measures. In acute alcoholism, with or without accompanying psychosis, the drug may occasionally be useful in combating pathologic intoxication. (In alcoholic psychoses best results are reported where the psychosis is of recent origin.)

In addition, the drug has been reported to be effective in the symptomatic treatment of orthostatic hypotension. It has also been used in spastic colitis, pyloric spasm, and certain other clinical conditions not mentioned above; but such use is not recommended.

Mixtures containing amphetamine sulfate have been exploited for use in obtaining weight reduction. However, in selected cases under the supervision of a physician amphetamine sulfate has been found useful to depress the appetite.

While the drug is useful in the treatment of various depressive states, evidence indicates that it is of little value in altering the course of the underlying psychosis in the major psychopathic conditions. Obviously, in severe depressive psychopathic cases, the patient should be institutionalized.

Results in the psychoneuroses are variable. In mild psychogenic disorders the use of the drug should be subordinated to efforts directed toward the correction of the underlying causes.

The use of amphetamine sulfate to alleviate sleepiness and fatigue by persons not under medical control is to be condemned. The danger lies in the elimination of the warning signal of fatigue in individuals who are overdoing, the possibility of habit formation on continued use, and the undesirable circulatory effects. Collapse has occurred in some cases when the drug has been so used. Except when administered under the strict supervision of the physician, its use is not recommended for developing a sense of exhilaration, increased energy and capacity for work; nor as a "pick-me-up" following temporary alcoholic overindulgence.

Because of the inherent pharmacological nature of amphetamine, the physician should be fully aware of the possibility that its administration may, in certain instances, produce overstimulation, restlessness, sleeplessness, and gastrointestinal disturbance; and that overdosage may be followed by chills, collapse, and syncope.

Caution should be exercised in administering the drug in the presence of hypertension or cardiovascular disease. Administration of amphetamine is contraindicated in patients manifesting anxiety, hyperexcitability, or undue restlessness. The possibility that deleterious effects may be produced from habituation to the drug, although cases of habit formation have only rarely been reported, must be kept in mind.

**Dosage.**—Since effective dosage varies considerably with the individual patient and with the condition being treated, initial doses should be small (5 mg., or less), and should be increased gradually until a definite effect manifests itself. The use of a small test dose is particularly important in the treatment of depressive states. In most cases, it is desirable to administer the drug in divided doses. To avoid interference with sleep, the final daily dose should ordinarily not be given later than 4 p. m. The usual therapeutic dosage range is from 5 to 30 mg., though larger doses are occasionally given. To depress the appetite in overweight, doses of 5 to 10 mg. three times daily, preferably administered one-half to one hour before each meal, are usually sufficient. The dosage should be adjusted to individual needs and should be the minimum amount of the drug necessary to produce the desired reduction of appetite. In no instance should it exceed 30 mg. daily. To minimize the possibility of initial overstimulation the physician should begin treatment with smaller doses, increasing them gradually until optimal results are achieved. (With light sleepers, it is best to administer the last daily dose not later than 4 P.M.)

SMITH, KLINE & FRENCH LABORATORIES

**Benzedrine Sulfate (Powder):**

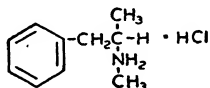
**Capsules Benzedrine Sulfate:** Amphetamine sulfate, 5 mg.

**Elixir Benzedrine Sulfate:** 355 cc. bottles. Each 5 cc. contains racemic amphetamine sulfate 2.5 mg. and alcohol 10 per cent.

**Tablets Benzedrine Sulfate:** Racemic amphetamine sulfate 5 mg. and 10 mg.

U. S. patent 1,879,003 (Sept. 27, 1932; expires 1949), 1,921,424 (Aug. 8, 1933; expires 1950). U. S. trademark 337,407.

***d*-DESOXYEPHEDRINE HYDROCHLORIDE.** — **Norodin Hydrochloride-Endo.**—The hydrochloride salt of the base, dextro-1-phenyl-2-methylaminopropane.—*d*-Phenylisopropylmethylamine hydrochloride.—*d*-1-Phenyl-2-methylaminopropane hydrochloride.—*d*-N-methylphenylisopropylamine hydrochloride.—*d*-N-methylamphetamine hydrochloride. The structural formula of *d*-desoxyephedrine hydrochloride may be represented as follows:



For tests and standards, see Section B.

When dried over sulfuric acid for 18 hours, it contains not less than 79.5 per cent nor more than 80.8 per cent of anhydrous *d*-desoxyephedrine, corresponding to not less than 98.9 per cent of *d*-desoxyephedrine hydrochloride.



**Actions and Uses.**—The actions of *d*-desoxyephedrine hydrochloride are essentially similar to those of amphetamine; they differ only in degree. It appears that the central stimulant effects may be slightly greater and the circulatory action slightly less than with amphetamine.

*d*-Desoxyephedrine hydrochloride may be used in the treatment of narcolepsy, in controlling oculogyric crises and various other manifestations of postencephalitic parkinsonism, as an adjunct in the treatment of alcoholism, and in the treatment of certain depressive conditions, especially those characterized by apathy and psychomotor retardation.

*d*-Desoxyephedrine has also been used as an adjunct in the treatment of obesity. It depresses the motility of the gastrointestinal tract and allays the sensation of hunger. It may assist some individuals in adhering to a strict dietary regime. It may also assist those individuals in whom over-eating is a response to a depressive state.

The contraindications to the use of *d*-desoxyephedrine are the same as those for amphetamine, namely hypertension and cardiovascular disease. The drug should not be administered within four hours before sleep is desired.

**Dosage.**—It is advisable to begin with a small dose of 2.5 mg. and, if necessary, increase the dose by increments of 2.5 mg. until the optimal response is obtained.

ENDO PRODUCTS, INC.

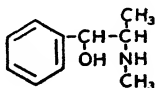
**Norodin Hydrochloride (Powder):** 1 Gm., 5 Gm. and 10 Gm. vials.

**Tablets Norodin:** 2.5 mg. and 5 mg.

**EPHEDRINE-U. S. P.**—“An alkaloid obtained from *Ephedra equisetina* Bunge, *Ephedra sinica* Stapf and other species of *Ephedra* (Fam. *Gnetaceae*), or produced synthetically. It is anhydrous, or contains not more than one-half molecule of water of hydration. Anhydrous Ephedrine contains not less than 98.5 per cent of  $C_{10}H_{15}NO$ . Hydrated Ephedrine contains not less than 94 per cent of  $C_{10}H_{15}NO$ .” U. S. P.

For description and standards see the U. S. Pharmacopeia under Ephedrine.

Ephedrine is an alkaloid first obtained by Nagai in 1887 from a Chinese herb, ma huang (*Ephedra equisetina*). Chemically, ephedrine is 1-phenyl-2-methylamino-propanol-1. Structurally, it is closely related to epinephrine, and like epinephrine it is levorotatory; but it is more stable. Its salts are, in general, soluble in water and in alcohol. The structural formula of ephedrine may be represented as follows:



**Actions and Uses.**—Ephedrine produces peripheral effects somewhat similar to those of epinephrine. However, it is difficult to explain fully its effects without postulating some central nervous action and some action on striated muscle as well as its direct stimulating effect on sympathetically innervated smooth muscle. In small doses ephedrine has a stimulating action on the heart, increasing the rate and the strength of contractions and raising the blood pressure. In large and toxic doses the drug has a depressant action on the heart muscle. It causes a rather lasting rise of blood pressure, on intravenous or intramuscular injection, due mainly to vasoconstriction. Other effects similar to those of epinephrine are dilatation of the bronchi and mydriasis after local or systematic administration. On local application to mucous membranes or wounds it contracts the capillaries to a moderate degree and thus diminishes hyperemia and reduces swelling. Ephedrine is used locally in the eye to dilate the pupils, and in the nostrils to shrink the congested mucosa in rhinitis and sinusitis. The systemic effects can be obtained by oral as well as by hypodermic or intramuscular administration. Ephedrine is useful against asthma, especially to prevent the attacks; but it often fails partially or completely. It is also used against hay fever and urticaria. It tends to produce symptoms of the anxiety complex. This may constitute a definite contraindication to its use. Its use in serious heart disease is considered unsafe. Ephedrine is used to sustain the blood pressure in spinal anesthesia and in some types of hypotension, but it is not thought that the drug is of any benefit in shock, circulatory collapse and hemorrhage. It is of limited value in preventing the muscle weakness of myasthenia gravis. It is without value in Addison's disease.

**Dosage.**—Salts of ephedrine are quite effective whether given orally, intramuscularly, intravenously, or by any other ordinary path of administration. For local application to mucous membranes it is used in 0.5 to 2 per cent solution of a salt of ephedrine; in ophthalmologic work it has been used in 4 per cent solution. Orally, the usual dose for adults is from 20 to 50 mg. every 3 to 4 hours.

**ABBOTT LABORATORIES**

**Ephedrine (Powder):** bulk.

**GANE AND INGRAM, INC.**

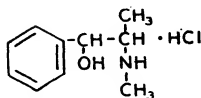
**Ephedrine (Powder):** bulk.

**MERCK & Co., INC.**

**Ephedrine (Powder):** bulk.

**EPHEDRINE HYDROCHLORIDE-U. S. P.**—"When dried at 100 C. for 3 hours, contains not less than 80.4 per cent and not more than 82.5 per cent of anhydrous ephedrine ( $C_{10}H_{15}NO$ ), corresponding to not less than 98 per cent

$C_{10}H_{15}NO.HCl$  U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Ephedrine Hydrochloride and The National Formulary under Ephedrine Hydrochloride Tablets.

*Actions and Uses.*—See general article, Ephedrine.

*Dosage.*—See general article, Ephedrine.

#### ABBOTT LABORATORIES

**Solution Ephedrine Hydrochloride, 3% :** Preserved with chlorobutanol, 0.5 per cent.

**Solution Ephedrine Hydrochloride 2½% and Procaine Hydrochloride 1% :** 2 cc. ampuls.

**Solution Ephedrine Hydrochloride 5% and Procaine Hydrochloride 1% :** 1 cc. and 2 cc. ampuls.

**Syrup Ephedrine Hydrochloride:** Contains ephedrine hydrochloride, 0.2195 Gm. in 100 cc. and alcohol 12 per cent.

**Tablets Ephedrine Hydrochloride:** 32.5 mg.

U. S. patent 1,260,289 (March 26, 1918; expired).

#### AMERICAN PHARMACEUTICAL Co., INC.

**Capsules Ephedrine Hydrochloride:** 25 mg. and 50 mg.

**Solution Ephedrine Hydrochloride, 3% :** 30 cc. bottle. Preserved with 0.5 per cent chlorobutanol.

#### GEORGE A. BREON & COMPANY, INC.

**Solution Ephedrine Hydrochloride 3% :** 29.5 cc. and 480 cc. bottles. 0.5 per cent chlorobutanol added as preservative.

#### ENDO PRODUCTS, INC.

**Capsules Ephedrine Hydrochloride:** 24 mg., 32.4 mg. and 49 mg.

#### GANE AND INGRAM, INC.

**Ephedrine Hydrochloride (Powder):** bulk.

#### ELI LILLY AND COMPANY

**Pulvules Ephedrine Hydrochloride:** 25 mg. and 50 mg.

**Solution Ephedrine Hydrochloride, 3%:** Preserved with chlorobutanol, 0.5 per cent.

**Syrup Ephedrine Hydrochloride:** Contains ephedrine hydrochloride, 0.22 Gm., in 100 cc. and alcohol 12 per cent; it is flavored with vanillin, benzaldehyde and tolu, and tinted with amaranth.

MERCK & Co., INC.

**Ephedrine Hydrochloride (Powder):** bulk.

PARKE, DAVIS & COMPANY

**Capsules Ephedrine Hydrochloride:** 25 mg. and 50 mg.

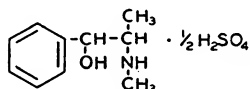
PITMAN-MOORE CO., DIVISION OF ALLIED LABORATORIES, INC.

**Capsules Ephedrine Hydrochloride:** 24 mg.

WARREN-TEED PRODUCTS COMPANY

**Capsules Ephedrine Hydrochloride:** 25 mg.

**EPHEDRINE SULFATE-U. S. P.**—"When dried at 100 C. for 3 hours, contains not less than 75.5 per cent and not more than 77.3 per cent of anhydrous ephedrine ( $C_{10}H_{15}NO$ )," corresponding to not less than 98 per cent of  $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$ . U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Ephedrine Sulfate and Ephedrine Sulfate Tablets and the National Formulary under Ephedrine Sulfate Ampuls, Ephedrine Sulfate Capsules, Ephedrine Sulfate Jelly, Ephedrine Sulfate Solution and Ephedrine Sulfate Syrup.

*Actions and Uses.*—See general article, Ephedrine.

*Dosage.*—See general article, Ephedrine.

ABBOTT LABORATORIES

**Capsules Ephedrine Sulfate:** 24 mg. and 50 mg.

**Solution Ephedrine Sulfate:** 25 mg. and 50 mg. 1 cc. ampuls.

**Solution Ephedrine Sulfate 3%:** Preserved with chlorobutanol, 0.5 per cent.

AMERICAN PHARMACEUTICAL CO., INC.

**Solution Ephedrine Sulfate, 3%:** 30 cc. bottle. Preserved with 0.5 per cent chlorobutanol.

**Capsules Ephedrine Sulfate:** 25 mg. and 50 mg.

GEORGE A. BREON & COMPANY, INC.

**Nasal Jelly Ephedrine Sulfate 1% with Sodium Chloride:** 15 Gm. collapsible tube. Ephedrine sulfate 1 per cent with sodium chloride 0.8 per cent in a water soluble boroglycerin jelly base.

BURROUGHS WELLCOME & Co., INC.

**Solution Ephedrine Sulfate:** 49 mg. in 1 cc. ampuls.

ENDO PRODUCTS, INC.

**Solution Ephedrine Sulfate:** 50 mg. in 1 cc. ampuls.

**Solution Ephedrine Sulfate, 3%:** 29.5 cc. bottle. Preserved with 0.5 per cent chlorobutanol.

**Tablets Ephedrine Sulfate:** 24 mg.

GANE AND INGRAM, INC.

**Ephedrine Sulfate (Powder):** bulk.

THE HARROWER LABORATORY, INC.

**Capsules Ephedrine Sulfate:** 24 mg. and 49 mg.

ELI LILLY AND COMPANY

**Solution Ephedrine Sulfate:** 25 mg. in 1 cc. and 50 mg. in 1 cc. ampuls.

**Elixir Ephedrine Sulfate:** Contains ephedrine sulfate, 0.44 Gm. in 100 cc. in a menstruum composed of alcohol 12 per cent, glycerin, sucrose and water, flavored with gluside, oenanthic ether, oil of orange, oil of coriander, oil of caraway, oil of lemon, oil of cassia, oil of anise, safrol and vanillin.

**Jelly Ephedrine:** Ephedrine sulfate, 1 Gm.; glycerin, 15 Gm.; tragacanth, 1 Gm.; eucalyptol, 0.1 Gm.; oil of wintergreen, 10 mg.; oil of dwarf pine needles, 10 mg.; sodium phosphate U. S. P., 0.16 Gm.; water to make 100 Gm.

**Pulvules Ephedrine Sulfate:** 25 mg. and 50 mg.

**Solution Ephedrine Sulfate 3%:** Preserved with chlorobutanol, 0.5 per cent.

**Syrup Ephedrine Sulfate:** Containing ephedrine sulfate, 0.22 Gm., in 100 cc. and alcohol 12 per cent; it is flavored with vanillin, benzaldehyde and tolu, and tinted with amaranth.

THE MALTBIE CHEMICAL COMPANY

**Nasal Jelly Ephedrine:** Ephedrine sulfate, 1 per cent, and sodium benzoate 0.5 per cent in a glycerite of tragacanth base.

THE S. E. MASSENGILL Co.

**Solution Ephedrine Sulfate, 3%:** 473 cc., 120 cc. and 30 cc. bottles. Preserved with 0.5 per cent chlorobutanol.

MERCK & Co., INC.

**Ephedrine Sulfate (*Powder*):** bulk.

THE WM. S. MERRELL CO., LOESER LABORATORY DIVISION

**Solution Ephedrine Sulfate:** 48 mg. in 1 cc. ampuls.

E. S. MILLER LABORATORIES, INC.

**Capsules Ephedrine Sulfate:** 25 mg. and 50 mg.

**Solution Ephedrine Sulfate:** 50 mg. in 1 cc. ampuls. Preserved with chlorobutanol 0.5 per cent.

THE NATIONAL DRUG COMPANY

**Capsules Ephedrine Sulfate:** 25 mg. and 50 mg.

PARKE, DAVIS & COMPANY

**Capsules Ephedrine Sulfate:** 25 mg. and 50 mg.

**Solution Ephedrine Sulfate:** 50 mg. in 1 cc. glaseptic ampuls.

PREMO PHARMACEUTICAL LABORATORIES

**Ephedrine Sulfate (*Powder*):** 15 Gm., 30 Gm. and 120 Gm.

**Capsules Ephedrine Sulfate:** 24 mg., 32 mg. and 50 mg.

WILLIAM H. RORER, INC.

**Solution Ephedrine Sulfate:** 50 mg. in 1 cc. ampuls.

SHARP & DOHME, INC.

**Solution Ephedrine Sulfate:** 50 mg. in 1 cc. ampuls. Preserved with 0.5 per cent of chlorobutanol.

**Capsules Ephedrine Sulfate:** 50 mg.

**Solution Ephedrine Sulfate 3%:** Preserved with chlorobutanol, 0.5 per cent.

SMITH-DORSEY COMPANY

**Capsules Ephedrine Sulfate:** 25 mg. and 50 mg.

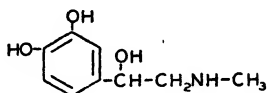
THE UPJOHN COMPANY

**Capsules Ephedrine Sulfate:** 25 mg. and 50 mg.

**Solution Ephedrine Sulfate:** 50 mg. in 1 cc. ampuls.

**EPINEPHRINE-U. S. P.—Adrenalin-Parke, Davis.—Suprarenalin-Armour. — Suprarenin-Winthrop-Stearns. — *Alpha*-(3,4-dihydroxy phenyl)-*Beta*-methylamino ethanol. —** Epinephrine, the active principle of the medullary portion of the suprarenal glands, is used extensively in surgery and to a lesser extent in medicine in the form of the 1 in 1,000 solution of epinephrine hydrochloride (Epinephrine Solution, U. S. P.). The

alkaloid may be prepared from suprarenal glands or synthesized by any of several methods. (The racemic epinephrine prepared chemically is only about half as active physiologically as natural epinephrine, but it can be resolved. Dextrorotatory epinephrine is almost inactive physiologically.) The structure formula of epinephrine may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Epinephrine, Epinephrine Inhalation, Epinephrine Injection and Epinephrine Solution.

**Actions and Uses.**—Epinephrine acts peripherally on a variety of structures by stimulating directly the effector cells innervated by the sympathetic nerves. Its most important actions consist of a constriction of the blood vessels of the skin, dilatation of blood vessels of the voluntary and heart muscles, and stimulation of the heart with an increase in cardiac output, a rise in systolic arterial pressure and a widening of pulse pressure. Relaxation of the bronchial muscles and also glycosuria follow intramuscular or hypodermic injection. Moderate doses, when given by mouth, have practically no action. However, in hypersensitive patients, such as those with thyrotoxicosis, the administration of epinephrine by mouth may occasionally produce typical effects. The effect of a single intravenous dose is fleeting.

Epinephrine is used locally for its vasoconstrictor action in hemorrhage, and in catarrhal and congestive conditions. It often relieves asthmatic paroxysms when used by hypodermic injection; because of the marked increase in vital capacity produced by the drug it is most valuable for treating a severe acute attack of asthma. If, however, asthmatic paroxysms are frequent it is generally advisable to use ephedrine with or in place of epinephrine. By parenteral injection epinephrine is used to treat serum sickness, anaphylaxis, the nitritoid reaction following arsphenamine therapy, urticaria, and angioneurotic edema. Intravenous injections are sometimes effective in anesthesia accidents (care being taken not to give an overdose) and in emergency cardiac failure as in drowning and electrocuting. It is of little or no value in Addison's disease. Epinephrine in the form of a 2 per cent solution of a salt of epinephrine has been used locally in the treatment of glaucoma with apparently favorable results in certain cases, while in other cases it appears to be ineffective.

Untoward reactions which frequently occur following administration of epinephrine consist of headache, anxiety, restlessness, tremors, dizziness, palpitation and respiratory difficulty. Hyperthyroid patients are especially susceptible to these responses.

Epinephrine is contraindicated in cyclopropane or chloroform anesthesia because of the danger of ventricular fibrillation. Con-

siderable caution should be exercised in using epinephrine in patients with cerebral arteriosclerosis, organic heart disease, angina pectoris and hyperthyroidism. The drug should not be used in shock.

The vasoconstrictor action of epinephrine is used to prolong the anesthetic effect of local anesthetics by retarding the circulation in the injected area thus hindering the removal of the anesthetic agent by too rapid absorption into the blood stream. In the same manner it is believed to lessen the toxicity of the local anesthetics by retarding their absorption into the general circulation.

Dilute aqueous solutions rapidly lose their strength, the deterioration being accompanied by a reddish or brownish discoloration.

To guard against too great a local ischemia, which may lead to local death of tissue, the concentration of epinephrine in the local anesthetic solution should not be greater than 1:50,000.

To guard against a possible systemic reaction due to absorption of epinephrine, the total dose of this drug injected with a local anesthetic solution at one time should never be greater than 1 mg. (1 cc.).

**Dosage.**—Hypodermically or intramuscularly from 0.06 to 1 cc. of a 1 in 1,000 solution of epinephrine hydrochloride. Locally, it is used in solution varying in strength from 1 in 15,000 to 1 in 1,000. Epinephrine is also used in solution; in ointment for application to mucous membranes, such as the eye or the nose, where a slower but more lasting action is desired; and in suppositories.

#### THE ARMOUR LABORATORIES

**Suprarenalin (Crystals):** 63 mg. vials. Epinephrine.

U. S. patent 829,220 (Aug. 21, 1906; expired).

#### PARKE, DAVIS & COMPANY

**Adrenalin (Crystals):** bulk.

**Inhalant Adrenalin with Chloretone 3%:** A glycerin solution containing 1 part of epinephrine (as epinephrine hydrochloride) in 1,000, 3 per cent of chloretone, 15 per cent of alcohol, and aromatics.

**Ointment Adrenalin:** Contains epinephrine hydrochloride equivalent to one part of epinephrine in 1,000 parts of oleaginous ointment base.

**Solution Adrenalin Chloride 1:2,600:** 1 cc. ampuls containing sterile solution 1 part of epinephrine hydrochloride in 2,600 parts of isotonic solution of sodium chloride, with not more than 0.1 per cent of sodium bisulfite as a preservative.

**Solution Adrenalin Chloride 1:10,000:** 1 cc. ampuls containing sterile solution 1 part of epinephrine hydrochloride in



10,000 parts isotonic solution of sodium chloride with not more than 0.1 per cent of sodium bisulfite as a preservative.

**Suppositories Adrenalin:** One part of epinephrine (as epinephrine hydrochloride) to 1,000 parts of oil of theobroma (cacao butter) and not more than 0.2 per cent of sodium bisulfite. Each suppository weighs about 1 Gm.

**Tablets Adrenalin:** 1 mg. epinephrine borate, yielding a 1 in 1,000 solution when dissolved in 1 cc. of water. Each tablet contains not more than 1 mg. of sodium bisulfite.

**Tablets Adrenalin:** 0.33 mg. Each contains 0.33 mg. epinephrine borate, yielding a 1 in 1,000 solution when dissolved in  $\frac{1}{3}$  cc. water. Each tablet contains not more than 0.33 mg. of sodium bisulfite.

U. S. patents 730,175, 730,176, 730,196, 730,197, 730,198 (June 2, 1903; expired); 753,177 (Feb. 23, 1904; expired). U. S. trademark 53,934.

#### THE UPJOHN COMPANY

**Epinephrine (Powder):** 65 mg. vials.

#### WILSON LABORATORIES

**Epinephrine (Crystals):** bulk.

#### WINTHROP-STEARNs, INC.

**Suprarenin Bitartrate (Powder):** 50 mg. ampuls. Each ampul contains epinephrine bitartrate 91 mg., equivalent to epinephrine 50 mg.

**Solution Suprarenin in Sesame Oil 1:500:** 1 cc. ampuls. Each cubic centimeter contains 2 mg. Suprarenin (base) in sesame oil.

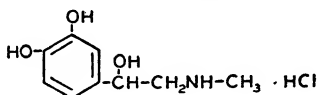
**Solution-Suprarenin Bitartrate 1:1,000:** 1 cc. ampuls and 30 cc. bottles. Each 1 cc. contains epinephrine bitartrate equivalent to epinephrine 1 mg., sodium chloride 6 mg. and sodium bisulfite not more than 2 mg. Chlorobutanol 0.5 per cent is contained in the bulk packages.

**Tablets Suprarenin Bitartrate:** 1 mg. Each tablet contains epinephrine bitartrate equivalent to 1 mg. of epinephrine with lactose 30 mg. and acetone sodium bisulfite not more than 0.67 mg.

**Tablets Suprarenin Bitartrate:** 20 mg. Each tablet contains epinephrine bitartrate 36.4 mg., equivalent to epinephrine 20 mg., with lactose 38.5 mg., and acetone sodium bisulfite not more than 0.1 mg.

U. S. patent 986,156 (March 7, 1911; expired). U. S. trademark 43,539; 74,280 (Chemical Foundation, Inc.).

**EPINEPHRINE SOLUTION-U. S. P. — Adrenalin Chloride Solution-Parke, Davis.—Suprarenalin Solution-Armour.**—"A solution of epinephrine in distilled water prepared with the aid of hydrochloric acid. It has a potency equivalent to a solution containing 1 Gm. of U. S. P. Epinephrine Reference Standard in each 1,000 cc." *U. S. P.* The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Epinephrine Solution.

*Actions and Uses.*—See Epinephrine.

*Dosage.*—See Epinephrine.

#### ABBOTT LABORATORIES

**Solution Epinephrine Hydrochloride 1:1,000:** 30 cc. safety container for parenteral or topical use contains sodium bisulfite 0.1 per cent and chlorobutanol 0.5 per cent as a preservative. Also available in 1 cc. ampuls containing sodium bisulfite 0.1 per cent as a preservative.

#### THE ARMOUR LABORATORIES

**Solution Suprarenalin 1:1,000:** 1 cc. ampuls, 5 cc., 10 cc. and 30 cc. vials for hypodermic use and 30 cc. bottles for topical use. Contains epinephrine hydrochloride 0.1 per cent, chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent in isotonic solution of sodium chloride.

U. S. patent 829,220 (Aug. 21, 1906; expired).

#### BARRY BIOLOGICAL LABORATORY, DIVISION OF BARRY LABORATORIES, INC.

**Solution Epinephrine Hydrochloride 1:1,000:** 30 cc. vials. Each cubic centimeter contains epinephrine U. S. P. 1 mg. in isotonic solution of sodium chloride with chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as preservatives.

#### GEORGE A. BREON & COMPANY, INC.

**Solution Epinephrine Hydrochloride 1:1,000:** 1 cc. ampuls. Contains chlorobutanol 0.5 per cent and sulfurous acid not more than 0.06 per cent in isotonic solution of sodium chloride.

#### BREWER & COMPANY, INC.

**Solution Epinephrine Hydrochloride 1:1,000:** 1 cc. ampuls. Each cubic centimeter contains epinephrine hydrochloride 1 mg. in isotonic solution of sodium chloride with sodium bisulfite 0.1 per cent.

**BRISTOL LABORATORIES, INC.**

**Solution Epinephrine Hydrochloride 1:1,000:** 1 cc. ampuls, 30 cc. vials for parenteral injection, and 30 cc. bottles for topical administration. Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as preservatives, in isotonic solution of sodium chloride.

**ENDO PRODUCTS, INC.**

**Solution Epinephrine Hydrochloride, 1:1,000:** 1 cc. ampuls and 30 cc. vials (rubber stoppered and cork stoppered). Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as a preservative, in isotonic solution of sodium chloride.

**LAKESIDE LABORATORIES, INC.**

**Solution Epinephrine Hydrochloride ,1:1,000:** 30 cc. vials. Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as a preservative, in isotonic solution of sodium chloride, saturated with carbon dioxide.

**LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.**

**Solution Epinephrine Hydrochloride 1:1,000:** 30 cc. vials for parenteral injection. Contains chlorobutanol 0.5 per cent and sodium bisulfite 0.1 per cent as preservatives.

**PARKE, DAVIS & COMPANY**

**Solution Adrenalin Chloride 1:1,000:** 1 cc. ampul contains epinephrine hydrochloride 0.1 per cent in isotonic solution of sodium chloride, with chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent as preservatives.

U. S. patents 730,175; 730,176; 730,196; 730,197; 730,198 (June 2, 1903, expired); 753,177 (Feb. 23, 1904; expired). U. S. trademark 53,934.

**THE UPJOHN COMPANY**

**Solution Epinephrine Hydrochloride 1:1,000:** 1 cc. ampuls and 30 cc. vials. Each cubic centimeter contains epinephrine 1.0 mg., sodium chloride 7.0 mg., sulfur dioxide (as sulfurous acid) not more than 0.6 mg., chlorobutanol not more than 5.0 mg., dissolved in distilled water saturated with carbon dioxide.

**U. S. STANDARD PRODUCTS Co.**

**Solution Epinephrine Hydrochloride 1:1,000:** 1 cc. ampuls and 30 cc. bottles for topical use. Contains chlorobutanol 0.5 per cent as a preservative.

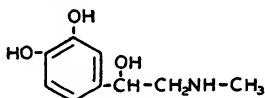
**WARREN-TEED PRODUCTS COMPANY**

**Solution of Epinephrine Hydrochloride 1:1,000:** 30 cc. rubber stoppered vials. Contains epinephrine hydrochloride 0.1 per cent, sodium bisulfite 0.1 per cent and chlorobutanol 0.5 per cent in isotonic solution of sodium chloride.

## WILSON LABORATORIES

**Solution Epinephrine Hydrochloride 1:1,000:** 30 cc. bottles and vials, for topical use. Contains chlorobutanol 0.5 per cent and sulfurous acid not more than 0.06 per cent as preservatives in isotonic solution of sodium chloride.

**EPINEPHRINE IN OIL SUSPENSION, 1:500.—Adrenalin in Oil, 1:500—Parke, Davis.**—Suspension of epinephrine base 1:500. A 0.2 per cent suspension, containing 1 part of epinephrine U. S. P. to 500 parts of vegetable oil. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Injections of solutions of epinephrine salts (1:1,000) are known to provide prompt but transient relief in the treatment of severe attacks of bronchial asthma by relaxation of the bronchial muscles. Recent evidence indicates that injections of vegetable oil suspensions of epinephrine base (1:500) delay and prolong the action of the drug and thus provide more sustained symptomatic relief in this condition as well as in certain cases of hay fever, urticaria, angioneurotic edema and serum sickness. The usual contraindications to epinephrine must be kept in mind. The preparation should not be given to the aged or to patients with hypertension, because of its prolonged pressor effects. Its sustained action may also prolong disagreeable side effects as well as serious reactions due to overdosage in less tolerant individuals. Local reactions due to irritation by the oil, especially when injected subcutaneously, have also been reported. For this reason it is recommended that it be administered intramuscularly and that particular attention be paid to the possibility of scar formation (fibrosis) at the sites of injection. Reactions from the epinephrine itself may be partially avoided by adequate resuspension (shaking) of any precipitate in the oil; the use of a dry syringe and needle, and precautions to prevent injecting directly into the blood stream by withdrawal of the syringe plunger to determine the location of the needle point in relation to a vessel before each injection and caution in the selection of the initial dose. The use of a small caliber needle to minimize trauma to blood vessels is also recommended. Intravenous injection is, of course, contraindicated.

**Dosage.**—Intramuscularly from 0.2 cc. to 1.5 cc. (0.4 mg. to 3.0 mg. epinephrine base) administered every eight to sixteen hours. The initial dose for adults should never exceed 0.5 cc. (1 mg. epinephrine base) and caution is necessary when subsequent doses larger than 1.0 cc. are employed because of the unusually large amount of active material introduced (1 cc. of the oil suspension 1:500 is the equivalent of 2 cc. of an epi-

nephrine solution 1:1,000) and its more prolonged action. Doses in excess of 1.5 cc. are not recommended.

#### ABBOTT LABORATORIES

**Suspension Epinephrine in Oil, 1:500:** 1 cc. ampuls. A suspension of 2 mg. of epinephrine in 1 cc. of purified peanut oil.

#### ENDO PRODUCTS, INC.

**Suspension Epinephrine in Oil, 1:500:** 1 cc. ampuls. A suspension of 2 milligrams of epinephrine in 1 cc. of peanut oil.

#### LAKESIDE LABORATORIES, INC.

**Suspension Epinephrine in Oil, 1:500:** 1 cc. ampuls. A suspension of 2 mg. powdered epinephrine crystals in 1 cc. of sesame oil.

#### PARKE, DAVIS & COMPANY

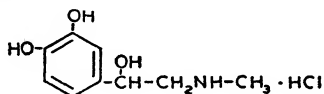
**Suspension Adrenalin in Oil 1:500:** 1 cc. ampuls. A suspension of 2 mg. of crystalline epinephrine in 1 cc. of peanut oil.

U. S. patents 730,175; 730,176; 730,196; 730,197; 730,198 (June 3, 1903; expired); 753,177 (Feb. 23, 1904; expired). U. S. trademark 53,934.

#### SMITH-DORSEY COMPANY

**Suspension Epinephrine in Oil, 1:500:** 1 cc. ampuls. A suspension of 2 milligrams of crystalline epinephrine in 1 cc. of peanut oil.

**EPINEPHRINE HYDROCHLORIDE SOLUTION, 1:100.—Adrenalin Chloride, 1:100—Parke, Davis.—Suprarenalin Solution, 1:100—Armour.**—A solution containing 1 part of epinephrine hydrochloride in 100 parts of isotonic solution of sodium chloride. The structural formula may be represented as follows:



**Actions and Uses.**—Injections of solutions of epinephrine (1:1,000) are known to be useful in the treatment of severe attacks of bronchial asthma. Recent evidence indicates that the oral inhalation of solution of epinephrine ten times stronger than those used by hypodermic injection gives relief in acute attacks of bronchial asthma when other measures fail. The physician should familiarize himself with the procedure before employing it in the treatment of his patients. It is absolutely essential that such treatment be instituted under the supervision of the physician and the patient warned of the dangers of using a solution of such strength carelessly. It is also necessary that the atomizer or nebulizer which is used in the administration of such solutions produce a fine mistlike spray free from minute

droplets. Every precaution must be taken to avoid confusion between this solution (1:100) and the official 1:1,000 epinephrine solution, since the 1:100 solution is not suitable for hypodermic use and should never be employed in that manner.

*Dosage.*—A definite dosage cannot be stated for the use of this preparation. It is obviously essential that the amounts used not exceed the minimal amount which will give effective relief. It is best to start with a single compression of the bulb of the atomizer or nebulizer until it is determined what dosage is adequate and safe. Its use should not be repeated until several minutes have passed so that the full effect of the inhalation can be observed before additional amounts are used.

#### THE ARMOUR LABORATORIES

**Solution Suprarenalin 1:100:** A solution of epinephrine hydrochloride 1.0 per cent, containing chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent as preservatives.

U. S. patent 829,220 (Aug. 21, 1906, expired).

#### BRISTOL LABORATORIES, INC.

**Solution Epinephrine Hydrochloride 1:100:** 5 cc. Contains epinephrine 10 mg., chlorobutanol 5 mg. and sodium bisulfite 1 mg. as preservative in isotonic solution of sodium chloride.

#### BURROUGHS WELLCOME & Co., INC.

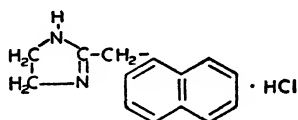
**Solution of Epinephrine Hydrochloride 1:100:** 5 cc. Contains epinephrine hydrochloride 1 per cent, chlorobutanol 0.5 per cent, sodium bisulfite 0.3 per cent and sodium chloride in isotonic solution.

#### PARKE, DAVIS & COMPANY

**Solution of Adrenalin Chloride 1:100:** 5 cc. vial. A solution of epinephrine hydrochloride 1.0 per cent, containing chlorobutanol 0.5 per cent and sodium bisulfite not more than 0.1 per cent as preservatives.

U. S. patents 730,175; 730,176; 730,196; 730,197; 730,198 (June 2, 1903, expired); 753,177 (Feb. 23, 1904, expired). U. S. trademark 53,934.

**NAPHAZOLINE HYDROCHLORIDE.**—Privine Hydrochloride-Ciba. — 2(1-naphthyl-methyl)imidazoline hydrochloride. The structural formula of privine hydrochloride may be written as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Naphazoline Hydrochloride is a vasoconstrictor, which, when applied to nasal mucous membranes, causes

a prolonged reduction of the local swelling and congestion. It is of value in the symptomatic relief of disorders of the upper respiratory tract such as nasal congestion of allergic and inflammatory origin, acute and chronic rhinitis, vasomotor rhinitis and acute and chronic rhinosinusitis. Care should be exercised, however, when vasoconstrictors are used for prolonged medication; naphazoline hydrochloride is no exception, although the rebound congestion of the mucosa which it may cause can be alleviated within a few days simply by discontinuing all nasal medication. Those who respond with rebound congestion may tolerate solutions weaker than the commonly used concentrations. The site of action is probably the effector cells innervated by the sympathetic nerves, a property assumed for epinephrine, although further work is needed to clarify this point. So far, there have been no reports proving that sufficient drug is absorbed following local application to increase the blood pressure, although this possibility should not be forgotten.

**Dosage.**—Adults may use several drops of the 0.1 per cent or 0.05 per cent solution, depending on the relief obtained and the sensitivity of the individual mucosa. Relief can be expected for several hours. Occasionally a smarting sensation and sneezing may develop.

For children, the 0.05 per cent solution is suggested.

Naphazoline hydrochloride solution is buffered to a  $p_H$  of 6.2-6.3. It is affected by aluminum and should not be used in atomizers made of this material. Otherwise the preparation can be employed by any of the conventional methods.

CIBA PHARMACEUTICAL PRODUCTS, INC.

**Nasal Jelly, Privine Hydrochloride 0.05%:** 20 Gm. tubes. Each 1 Gm. contains naphazoline hydrochloride 0.5 mg. in a buffered water soluble base containing glycerin, tragacanth and aromatics with Merthiolate 0.01 mg. as a preservative.

**Solution Privine Hydrochloride 0.1% (For Adults Only):** 30 cc. and 480 cc. bottles. Each 100 cc. contains privine hydrochloride 100 mg., exsiccated sodium phosphate 0.258 Gm., sodium chloride 0.324 Gm., potassium chloride 0.223 Gm. and potassium biphosphate 0.742 Gm., preserved with Merthiolate 1:100,000.

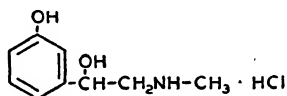
**Solution Privine Hydrochloride 0.05% (For Children):** 30 cc. and 480 cc. bottles. Each 100 cc. contains privine hydrochloride 50 mg., exsiccated sodium phosphate 0.258 Gm., sodium chloride 0.331 Gm., potassium chloride 0.223 Gm. and potassium biphosphate 0.742 Gm., preserved with Merthiolate 1:100,000.

U. S. patent 2,161,938.

U. S. trademark 398,004.

**PHENYLEPHRINE HYDROCHLORIDE.** — **Neo-Synephrine Hydrochloride-Winthrop-Stearns.**—laevo - $\alpha$ -hydroxy- $\beta$ -methylamino-3-hydroxy ethylbenzene hydrochloride. 1-(*m*-hydroxyphenyl)-2-methylaminoethanol hydrochloride.—The

hydrochloride of the laevo isomer of a synthetically prepared derivative of phenylethylamine having the formula shown below.



For tests and standards, see Section B.

*Actions and Uses.*—Phenylephrine hydrochloride is a vasoconstrictor and is active as a vasopressor when administered orally. It is more powerful in vasoconstrictive ability than synephrine tartrate, and possesses a relatively low toxicity. Applied to mucous membranes it causes contraction of the small blood vessels, thus reducing swelling and congestion of such membranes. Phenylephrine hydrochloride may be useful in the symptomatic treatment of the nasal congestion accompanying disorders of the upper respiratory tract such as sinusitis, vasomotor rhinitis and hay fever. In surgery the drug is useful for injection, in combination with a soluble local anesthetic, to retard the systemic absorption of the anesthetic and to prolong its action by local vasoconstriction. It may be injected alone for vasopressor effects as a preliminary or supportive measure to combat acute hypotension in spinal anesthesia. It may be similarly employed in other acute hypotensive states due to peripheral circulatory collapse (vasomotor failure), but the present evidence does not justify its use in true shock where vasomotor activity is unimpaired and the fall in blood pressure is mainly the result of the loss in circulating blood volume. Its value as a cardiac stimulant is at present conjectural. It may also be used as a mydriatic in the eye preliminary to fundoscopic examination and in conjunction with cycloplegics in the detection of refractive errors and as an aid in the prevention or freeing of posterior synechiae; and temporarily, as a vasoconstrictor to attempt to lower intraocular tension in certain cases of glaucoma when this effect is not counteracted by dilatation of the pupil.

*Dosage.*—For topical application to the nasal mucous membrane the 0.25 per cent solution is ordinarily used. The 1 per cent solution, diluted with an equal volume of isotonic solution of sodium chloride or Ringer's solution, may be used when a stronger preparation is desired. For surgical and dental anesthesia, it may be diluted in the proportion of 0.3 to 0.5 cc. of the 1 per cent solution to 10 cc. of a 2 per cent procaine hydrochloride solution. For parenteral injection, 0.1 to 1.0 cc. of the 1 per cent solution. Initial dose should not exceed 0.5 cc. (5 mg.) and subsequent doses should not be administered at intervals less than 10 to 15 minutes. The intravenous dose when necessary should be about one-tenth the subcutaneous or intramuscular dose. As a mydriatic, one or two drops of the 1 per cent solution or emulsion or the 2½ per cent ophthalmic solution; as



a temporary vasoconstrictor in the eye and strong mydriatic for freeing posterior synechiae, one drop of the 10 per cent emulsion or the 10 per cent solution. The  $\frac{1}{8}$  per cent ophthalmic solution may be used as a decongestant for minor irritations of the conjunctiva. Preparations of phenylephrine hydrochloride are incompatible with butacaine, but other local anesthetics may and should be used beforehand to reduce the irritation produced by the 10 per cent solution or emulsion. The  $\frac{1}{8}$  per cent, the  $2\frac{1}{2}$  per cent and the 10 per cent ophthalmic solutions contain, in addition to other ingredients, 0.001 per cent of Aerosol OT 100 (dioctyl ester of sodium sulfosuccinate). Phenylephrine hydrochloride is relatively stable in alkaline solutions; it may be sterilized by boiling.

WINTHROP-STEARNs, INC.

**Emulsion Neo-Synephrine Hydrochloride 1%:** 15 cc. bottle. Phenylephrine hydrochloride 1 per cent, sodium benzoate 0.4 per cent in a mineral oil and water emulsion containing acacia; preserved with chlorobutanol 0.5 per cent.

**Emulsion Neo-Synephrine Hydrochloride 10%:** 3 cc. bottle. Phenylephrine hydrochloride 10 per cent, sodium benzoate 0.4 per cent in a mineral oil and water emulsion containing acacia; preserved with sodium bisulfite 0.1 per cent, ascorbic acid 1 per cent and chlorobutanol 0.5 per cent.

**Jelly Neo-Synephrine Hydrochloride, 0.5%:** Phenylephrine hydrochloride, 0.5 per cent and sodium chloride 0.5 per cent, incorporated in a jelly-like bland base composed of tragacanth, chondrus, glycerin and water. Sodium benzoate 0.45 per cent is present as preservative. The product is supplied in collapsible tube containers.

**Solution Neo-Synephrine Hydrochloride,  $\frac{1}{8}$ %:** 15 cc. phenylephrine hydrochloride  $\frac{1}{8}$  per cent, sodium chloride 1.1 per 1.1 per cent, boric acid 1.5 per cent Aerosol OT 100, 0.001 per cent, boric acid 1.5 per cent Aerosol OT 100, 0.001 per cent, sodium citrate 0.441 per cent with chlorobutanol 0.4 per cent and sodium bisulfite 0.1 per cent as preservatives in an aqueous solution.

**Solution Neo-Synephrine Hydrochloride, 0.25%:** 29.5 cc., 118.3 cc. and 473 cc. bottles. Phenylephrine hydrochloride 0.25 per cent, sodium benzoate 0.1 per cent, and sodium chloride 0.65 per cent and sodium bisulfite 0.1 per cent in distilled water.

**Solution Neo-Synephrine Hydrochloride, 1%:** 29.5 cc., 118.3 cc. and 473 cc. bottles. Phenylephrine hydrochloride 1 per cent, sodium benzoate 0.1 per cent, and sodium chloride 0.5 per cent and sodium bisulfite 0.1 per cent in distilled water.

**Solution Neo-Synephrine Hydrochloride, 1%: (for Parenteral Use):** 5 cc. vial and six 1 cc. ampuls. A sterile solution of phenylephrine hydrochloride 1 per cent, sodium bisulfite 0.1 per cent and sodium chloride 0.6 per cent, in distilled water.

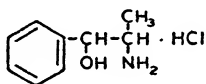
**Solution Neo-Synephrine Hydrochloride, 2½%:** 15 cc. phenylephrine hydrochloride 2½ per cent, sodium citrate 0.441 per cent, Aerosol, OT 100, 0.001 per cent boric acid 0.44 per cent, chlorobutanol 0.4 per cent and sodium bisulfite 0.1 per cent as preservatives in an aqueous solution.

**Solution Neo-Synephrine Hydrochloride, 10%:** 4 cc. phenylephrine hydrochloride 10 per cent, sodium citrate 0.441 per cent, Aerosol, OT 100, 0.001 per cent, boric acid 0.44 per cent, chlorobutanol 0.4 per cent and sodium bisulfite 0.1 per cent as preservatives in an aqueous solution.

**Solution Neo-Synephrine 0.25% in Isotonic Solution of Three Chlorides (with Aromatics):** 29.5 cc. and 473 cc. bottles. Phenylephrine hydrochloride 0.25 per cent, sodium sulfite not more than 0.11 per cent, with camphor, menthol and eucalyptol in isotonic solution of three chlorides.

U. S. patent 1,932,347 and 1,954,389 (April 10, 1934; expires April 10, 1951). U. S. trademark 90,142.

**PHENYLPROPANOLAMINE HYDROCHLORIDE**  
—Propadrine Hydrochloride.—Sharp & Dohme.—The hydrochloride of *racemic*-1-phenyl-2-aminopropanol.—Propadrine hydrochloride is the monohydrochloride of a base differing from ephedrine by having no methyl group on the amino nitrogen. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Phenylpropanolamine hydrochloride acts similarly to ephedrine. When applied locally, in the form of a 1 per cent aqueous solution or 0.66 per cent jelly, it produces constriction of the capillaries, thereby shrinking the swollen mucous membranes. It is said that its action is somewhat more prolonged than that of ephedrine. It is also claimed that the anxiety complex is not so apt to ensue with phenylpropanolamine hydrochloride as with ephedrine.

**Dosage.**—As a spray or instillation, 1 per cent aqueous solution or application of 0.66 per cent jelly locally; orally, as a 24 mg. capsule every two to four hours as indicated. Although no toxic effects have been noted, continued overdosage should be avoided as with other vasoconstrictors.

SHARP & DOHME, INC.

**Elixir Propadrine Hydrochloride:** Each 30 cc. contains propadrine hydrochloride 0.13 Gm. in a menstruum composed of alcohol 16 per cent, glycerin, sucrose and water, flavored with oil sweet orange, fluidextract licorice, and oil ceylon cinnamon, and colored with carmoisin (certified) and caramel.

**Capsules Propadrine Hydrochloride:** 24 mg. and 48 mg.

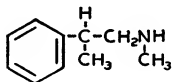
**Propadrine Hydrochloride Nasal Jelly, 0.66%:** Marketed in one-half ounce nasal tip collapsible tubes containing 0.66 per cent propadrine hydrochloride, with sodium chloride, menthol, thymol, and oil of lavender in a water-soluble base; chlorobutanol 0.5 per cent is added as preservative.

**Solution Propadrine Hydrochloride, 3%:** An aqueous solution containing 1 per cent phenylpropanolamine hydrochloride and made isotonic by the addition of 0.58 per cent sodium chloride; chlorobutanol 0.5 per cent is added as a preservative.

**Solution Propadrine Hydrochloride, 3%:** An aqueous solution containing 3 per cent phenylpropanolamine hydrochloride and 0.5 per cent chlorobutanol as a preservative.

U. S. patent 1,989,093 (Jan. 29, 1935; expires 1952). Propadrine is a U. S. registered trademark, but the firm disclaims any proprietary rights to the name.

**PHENYLPROPYLMETHYL AMINE — Vonedrine-Merrell.** — Racemic  $\beta$ -phenyl-N-propylmethylamine. — Racemic 1-methylamino-2-phenylpropane. —  $\beta$ -Methylaminocuniene. — 1-Methylamino-2-methyl-2-phenylethane. — The N-monomethyl derivative of  $\beta$ -phenyl-n-propylamine. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Phenylpropylmethyl amine base is volatile and therefore effective by inhalation, serving as a nasal vasoconstrictor. Its use is claimed to produce little or no evidence of irritation, local tissue reactions or central nervous system and cardiovascular stimulation.

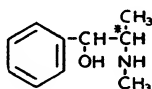
**Dosage.**—In using the phenylpropylmethyl amine Inhaler one long inhalation through each nostril is usually sufficient. This may be repeated as needed, although until more information is available in the entire field of sympathomimetic amine compounds, especially those used locally as nasal vasoconstrictors, the usual care concerning such compounds should be exercised.

## THE WM. S. MERRELL COMPANY

**Inhaler Vonedrine:** Each inhaler contains at the time of manufacture not less than 0.250 Gm. of beta-phenyl-N-propyl-methylamine and aromatics.

U. S. trademark 406,970.

**RACÉPHEDRINE.** — *Racemic* Ephedrine. — *Racemic*-1-Phenyl-2-methylaminopropanol-1. The structural formula may be represented as follows:



For tests and standards, see Section B.

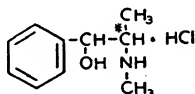
*Actions and Uses.*—The same as those of l-ephedrine.

*Dosage.*—From 30 to 50 mg.

GANE'S CHEMICAL WORKS, INC.

**Racephedrine (Crystals):** bulk.

**RACÉPHEDRINE HYDROCHLORIDE.** — *Racemic* Ephedrine Hydrochloride. — *Racemic*-1-Phenyl-2-methylaminopropanol-1. The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—The same as those of l-ephedrine hydrochloride.

*Dosage.*—From 30 to 50 mg.

GANE'S CHEMICAL WORKS, INC.

**Racephedrine Hydrochloride (Crystals):** bulk.

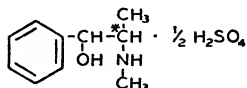
THE UPJOHN COMPANY

**Racephedrine Hydrochloride (Powder):** 120 Gm. bottles.

**Capsules Racephedrine Hydrochloride:** 25 mg.

**Solution Racephedrine Hydrochloride 1% in Ringer's Solution:** Contains in each 100 cc. racephedrine hydrochloride-N. N. R., 1 Gm., chlorobutanol, 0.5 Gm., sodium chloride, 0.86 Gm., potassium chloride, 30 mg., and calcium chloride, 33 mg. dissolved in distilled water.

**RACÉPHEDRINE SULFATE.**—*Racemic* Ephedrine Sulfate.—*Racemic*-1-Phenyl-2-Methylaminopropanol-1. The structural formula may be represented as follows:



For tests and standards, see Section B.

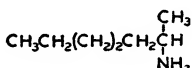
*Actions and Uses.*—The same as those of 1-ephedrine sulfate.

*Dosage.*—From 30 to 50 mg.

GANE'S CHEMICAL WORKS, INC.

**Racephedrine Sulfate (Crystals):** bulk.

**TUAMINE-Lilly.**—*Racemic* 2-aminoheptane.—The structural formula of 2-aminoheptane is:



For tests and standards, see Section B.

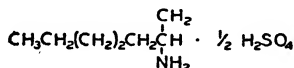
*Actions and Uses.*—Tuamine produces vasoconstrictive action and is a member of the group of compounds known as sympathomimetic amines. Inhalation of the vapors provides an effective method of treatment for acute rhinologic conditions and is of added usefulness when prolonged and repeated medication is necessary (*see also general monograph on sympathomimetic amines*). It should be used with caution by those who have cardiovascular disease. It is made available in an "inhaler" type of device.

*Dosage.*—One or two gentle inhalations through each nostril, repeated at hourly intervals if needed.

ELI LILLY & Co.

**Inhaler Tuamine:** Each inhaler contains at the time of packing 2-aminoheptane carbonate, equivalent to 325 mg. of 2-aminoheptane, menthol, 32 mg. and ylang ylang oil, 65 mg.

**TUAMINE SULFATE-Lilly.**—2-aminoheptane sulfate.—The formula of 2-aminoheptane sulfate is:



For tests and standards, see Section B.

*Actions and Uses.*—A 1 per cent solution of this compound exceeds the vasoconstrictive effects of a similar concentration of

ephedrine, while 0.5 per cent has been found to produce about equal vasoconstrictor action. The duration of effect, when compared to that of ephedrine, is prolonged.

**Dosage.**—A 1 per cent solution may be applied to the mucous membranes of infants and adults by spray, dropper or tampon and is usually adequate for routine treatment. A 2 per cent solution, best applied by pledgets of cotton, may be used for operative procedures, diagnostic examination and to meet other special circumstances. For displacement therapy, a 0.2 per cent solution can be used.

ELI LILLY & Co.

**Solution Tuamine Sulfate, 1%:** 30 cc. and 475 cc. bottles. Each 100 cc. contains Tuamine Sulfate 1.0 Gm., potassium phosphate monobasic 0.68 Gm., sodium chloride 90 mg., methyl parahydroxybenzoate 26 mg. and propyl parahydroxybenzoate 14 mg.

**Solution Tuamine Sulfate, 2%:** 60 cc. and 475 cc. Each 100 cc. contains Tuamine Sulfate 2.0 Gm., potassium phosphate monobasic 0.68 Gm., methyl parahydroxybenzoate 26 mg. and propyl parahydroxybenzoate 14 mg.

### Sympatholytic Agents

An anti-sympathomimetic (sympatholytic) agent is a drug whose effects on the body resemble the effects of cutting the sympathetic (thoracolumbar visceral efferent) nerve supply to various parts. Such a drug would be the antagonist of epinephrine; it would slow the heart, lower blood pressure by extensive vasodilation, increase gastrointestinal muscle tone and so on, by antagonizing the sympathetic nervous mechanisms.

Unfortunately no good example of this class is in common use. Various well-known preparations of ergot exhibit this type of action in some degree; they are described in the chapter on Ecboics. In addition, certain other substances may prevent the sympathomimetic action of epinephrine (adrenolytic effect) or prevent the effector response to sympathetic nerve stimulation (sympatholytic effect) or both.

Among the best-studied compounds synthesized by Fourneau are the two following:

F 933 (Piperidino-methyl-3-benzodioxane). This substance appears to be adrenolytic but not sympatholytic.

F 883 (Diethylaminomethyl-3-benzodioxane). This substance is reported to be both adrenolytic and sympatholytic.

There are other compounds in this series. None is useful clinically except under very special circumstances, mainly because of unpleasant or serious side-reactions on the central nervous system. Experimental reports suggest that dibenzyl-b-chlorethylamine (Dibenamine hydrochloride) or its derivatives may prove to be clinically useful adrenolytic and sympatholytic drugs effective by all routes of administration.

Drugs exhibiting this action include preparations of ergot which are described in the chapter on oxytocics.

### Parasympathomimetic Agents

A parasympathomimetic agent is a drug whose effects on the body resemble those seen when parasympathetic (craniosacral efferent) nerves are stimulated electrically. The effect most studied is probably the vagal inhibition of the heart. Pilocarpine, physostigmine, and acetylcholine are classed as parasympathomimetic because they slow the heart in much the same way as does the application of tetanizing current to the peripheral end of the cut vagus nerve.

It is now believed that acetylcholine is the common factor in many of these processes. When injected intravenously, it has a very powerful but transient parasympathomimetic effect; it acts so briefly because it is so promptly rendered inactive by hydrolysis with cholinesterase. The electrical stimulation of parasympathetic nerves causes the appearance of acetylcholine at the neuromuscular junctions; presumably acetylcholine appears regularly during the spontaneous functioning of the postganglionic fibers of the parasympathetic nerves, and is regularly kept from accumulating by the cholinesterase. Physostigmine is known to act by opposing the cholinesterase, and this fact makes physostigmine a parasympathomimetic drug. In the case of pilocarpine, muscarine, and some others, however, it has been necessary to suppose that they act directly on the same receptive structure as does acetylcholine. Various choline derivatives have been synthesized that are sufficiently stable in the presence of cholinesterase to produce useful effects of parasympathetic activity. Unlike acetylcholine, some are effective when administered orally and do not share its "nicotine" action. Methacholine is perhaps the best example of this class.

The typical parasympathetic effects, in addition to cardiac inhibition, are vasodilation in certain areas, miosis, and increased gastro-intestinal motion and secretion.

A recent addition to the group of parasympathomimetic drugs is di-isopropylfluorophosphate, which surpasses physostigmine and neostigmine in exerting a powerful inhibition on cholinesterase. It produces, for instance, a prolonged miosis which may prove helpful in the treatment of glaucoma.

### Acetyl-beta-methylcholine

Acetyl-beta-methylcholine is a choline derivative with sufficient stability within the body so that it may be employed in certain conditions in which the effects of parasympathetic stimulation are desirable. Its actions resemble the "parasympathetic" actions of acetylcholine with little or none of the latter's "nicotine" effect. It exerts a depressant effect at the sinoauricular node, auricular musculature and auriculoventricular node and bundle of the heart and stimulates gastrointestinal peristalsis. The bradycardia induced by the drug is blocked by quinidine, which also antagonizes its prolongation of auriculoventricular

conduction. It also produces a general vasodilatation of blood vessels which are not known to be innervated by parasympathetic nerves, with a subsequent fall in blood pressure. The drug may therefore be regarded as a physiological antagonist to epinephrine. All its effects are intensified and prolonged by physostigmine and prostigmine through their inhibition of cholinesterase but are quickly and completely abolished by atropine.

Unlike acetylcholine, the drug is capable of exerting a physiological effect when administered orally. When injected subcutaneously its actions appear to be more prolonged than those of acetylcholine, although the effect on the heart rate and blood pressure persists for only a few minutes. Its intravenous injection is dangerous.

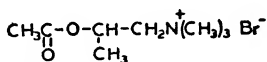
Crystalline water-soluble salts of the base, acetyl-beta-methylcholine, are employed to produce the effects of the drug. The salts are more or less hygroscopic, and if this tendency is extreme, as in the case of the chloride, the crystals must be protected from atmospheric moisture until placed in solution. Acetyl-beta-methylcholine chloride is therefore not suitable for oral administration in crystalline form but should be given in solution. The entire contents of containers of this salt should be put into solution immediately when these are once opened. Solutions of acetyl-beta-methylcholine chloride are fairly stable and will keep for at least two or three weeks. They are relatively stable to heat and may be refrigerated to delay mold growth.

The application of aqueous solutions of acetyl-beta-methylcholine chloride by the method of ion transfer (iontophoresis) to introduce this salt into the tissues by means of direct (galvanic) current is recognized as the best means to obtain the local effects of the drug on the extremities. General (systemic) effects are produced by this method but are less pronounced than when the drug is administered orally or by injection. The systemic effects produced in this way have not been observed to be of a serious or dangerous nature.

The following precautions should be observed in the administration of the drug: (1) Never administer intravenously because of the danger of cardiac arrest; (2) consider bronchial asthma, hyperthyroidism, coronary occlusion and any severe illness as contraindications; (3) avoid massage at the site of injection, except where this may be necessary to determine when a further injection is needed, and then only gently and with due caution; (4) advise recumbence during injection to avoid possible fainting; (5) the method of ion transfer (iontophoresis) should be employed only by those specially trained in such application and should not under any circumstances be used directly over ulcers or open wounds and only with care over scar tissue; extreme care is necessary to prevent burns by galvanism and the essentials of the "Safety Rules in Galvanism" outlined by Kovacs (Principles and Practice of Physical Therapy, vol. III, pp. 10 and 11) should be followed in the administration of the drug by this method; (6) therapy by any method of administration is contraindicated when grave side reactions occur.



**METHACHOLINE BROMIDE**—**Mecholyl Bromide-Merck**.—Acetyl-beta-methylcholine bromide.—Trimethyl-beta-acetoxy-propyl-ammonium bromide.—The acetyl ester of beta-methylcholine bromide. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions of methacholine bromide are the same as for methacholine chloride, but because it is less hygroscopic than the latter salt, it is suitable for oral use in tablet form for the treatment of those conditions in which this route of administration of the drug is recognized. Claims for the use of methacholine bromide other than by oral administration are not permissible and it should be kept in mind that for those skilled in the technic of ion transfer (iontophoresis) the local application of the chloride by this method is generally to be preferred in the treatment of chronic ulcers, scleroderma, Raynaud's disease and other vasospastic conditions of the extremities, except possibly the management of vascular spasm from exposure to moderate cold.

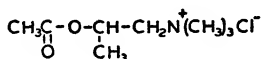
**Dosage.**—Methacholine bromide is administered in doses of 0.2 to 0.6 Gm. (one to three tablets) two or three times daily; 50 mg. to 0.1 Gm. ( $\frac{1}{4}$  to  $\frac{1}{2}$  tablet) may be sufficient to overcome vascular spasm due to moderate exposure to cold, but in chronic ulcers, scleroderma and Raynaud's disease the larger doses are required. With patients in whom a total daily dose of 2 Gm. (10 tablets) of the drug is not effective, the oral method of treatment should be abandoned in favor of the use of methacholine chloride by subcutaneous administration or local application by the method of ion transfer (iontophoresis).

**MERCK & Co., Inc.**

**Tablets Mecholyl Bromide: 0.2 Gm.**

U. S. patent 2,040,146 (May 12, 1936; expires 1953). U. S. trademark 318,783.

**METHACHOLINE CHLORIDE-U. S. P.**—**Mecholyl Chloride-Merck**.—Acetyl-beta-methylcholine chloride.—Trimethyl-beta-acetoxy-propyl-ammonium chloride.—The acetyl ester of beta-methylcholine chloride having the following formula:



For description and standards see the U. S. Pharmacopeia under Methacholine Chloride, Methacholine Chloride Capsules and Methacholine Chloride Injection.

**Actions and Uses.**—Methacholine chloride is useful in the treatment of selected cases of paroxysmal auricular tachycardia not responding to the usual therapeutic measures, by subcutaneous injection only, in the palliative local treatment of chronic rheumatoid (atrophic) arthritis by the method of ion transfer (iontophoresis) only, and in the treatment of chronic ulcers, Raynaud's disease, scleroderma and other vasospastic conditions of the extremities, preferably by the local method of ion transfer (iontophoresis) but also by oral or subcutaneous administration when the former cannot be employed. For the prevention of attacks of paroxysmal auricular tachycardia the drug is inferior to quinidine. It is of no apparent value in the treatment of other forms of tachycardia in auricular fibrillation. The possibility of inducing transitory heart block, to be followed by resumption of normal rhythm, should be kept in mind. Claims for the use of the drug in the treatment of bladder dysfunction, abdominal distention, atonic constipation, pelvic inflammation, functional dysmenorrhea, atropic rhinitis, glaucoma and hypertension are not warranted on the basis of existing clinical evidence. (Also see preceding article, methacholine bromide.)

**Dosage.**—Considerable variation in the oral dosage requirements is to be expected because methacholine chloride is to some extent destroyed by the gastric juice. The therapeutically effective oral dose usually ranges from 0.2 to 0.5 Gm. two or three times a day, administered by dissolving in a little water which may be added to milk to disguise the bitter taste. In overcoming vascular spasm due to moderate exposure to cold, oral doses of from 50 mg. to 0.1 Gm. have been found to be effective. In Raynaud's disease, scleroderma and ulcers the effective oral dose may be somewhat higher.

The subcutaneous dose should be limited to 10 mg. on the first injection to test the patient's tolerance. If well tolerated, the dose may be cautiously increased up to 25 mg. This dose is usually adequate for injection when this method of administration is employed in the treatment of Raynaud's disease, scleroderma, chronic ulcers and other vasospastic conditions of the extremities. In paroxysmal auricular tachycardia from 20 mg. to 40 mg. is injected subcutaneously. If a second injection is required, it is advisable to wait about ten to twenty minutes until the effect of the first has disappeared, and then only after cautious gentle massage at the site of the first injection. Cumulative, or overdosage, effects may be quickly abolished by an injection of atropine sulfate 0.6 mg.

For application of methacholine chloride by the method of ion transfer (iontophoresis) it is customary to use a 0.2 to 0.5 per cent (1:500 to 1:200) solution of the drug in distilled water. The solution is applied by moistening the positive electrode fabric which is placed over or near the part to be treated. The strength and duration of the galvanic current regulates the dosage and should always be applied gradually and within the point of comfortable tolerance by the patient. The patient

should be instructed to report any sensation of excessive heat or burning. If this occurs, the treatment should be stopped and an inspection made to determine if an electrode is improperly placed. The initial treatment should not exceed 5 to 10 milliamperes for thirty minutes. Subsequent treatments usually require from 25 to 30 milliamperes applied for twenty to thirty minutes. Each treatment should be restricted to a limited area such as one hand or one joint when several parts are involved. Three or four days is considered the most satisfactory interval between treatments. The number of treatments necessary to obtain results varies with the patient and with the type of lesion. In Raynaud's disease and scleroderma, ten or more treatments may be necessary to secure improvement; in chronic rheumatoid arthritis the treatments may be reduced to intervals of a week after the first four to six treatments; in varicose indolent and gangrenous ulcers, treatments may be given daily at the start to promote granulation of tissue and then reduced after the first few treatments to two or three times a week. During treatments by ion transfer (iontophoresis) the patient should be covered and protected from drafts and for about thirty minutes after each treatment should remain quiet and be kept warm before being permitted to resume protected activity.

Idiosyncrasy to methacholine chloride may result in difficulty in breathing. If this is noted the treatment should be stopped and the patient raised to a sitting position. If untoward symptoms do not subside, atropine sulfate should be given hypodermically at once.

MERCK & Co., INC.

**Mecholyl Chloride (Powder):** 1 Gm. and 10 Gm. bottles for the preparation of solutions for oral administration and for ion transfer (iontophoresis).

**Mecholyl Chloride (Powder):** 25 mg. ampul for the preparation of solutions for subcutaneous injection.

U. S. patent 2,040,146 (May 12, 1936; expires 1953). U. S. trademark 318,783.

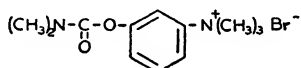
### Neostigmine

Pharmacologic experiments indicate that the neostigmine component of neostigmine compounds possesses some of the properties of the closely allied drug physostigmine. Its actions and uses, therefore, are similar to those of physostigmine, over which it has the advantage of being more stable. Apparently, it is as active as physostigmine in stimulating intestinal peristalsis and has a similar but somewhat diminished miotic activity. There is no satisfactory evidence that the symptoms produced by toxic doses of neostigmine salts are any less severe than those produced by comparable doses of physostigmine or its salts. This latter fact becomes especially important when it is considered that neostigmine preparations are used by subcutaneous and intramuscular injection, since the neostigmine component is from

four to six times as toxic as physostigmine when injected subcutaneously in the rabbit. Atropine is the antidote to neostigmine. Neostigmine preparations are used for the prevention of atony of the intestinal and bladder musculature, and for the symptomatic control of myasthenia gravis. Their use for the prevention and treatment of intestinal and bladder atony is based on activity as a vagotonic agent; their anti-curare-like action is the basis of application in the symptomatic treatment of myasthenia gravis. The drug is also credited with mild laxative action but its use solely for that purpose is not advisable.

Neostigmine is available only in the form of its salts.

**NEOSTIGMINE BROMIDE-U. S. P.—Prostigmin Bromide-Hoffmann-LaRoche.**—"When dried for 3 hours at 100 C., contains not less than 98 per cent of  $C_{12}H_{19}BrN_2O_2$ ." U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Neostigmine Bromide and Neostigmine Bromide Tablets.

**Actions and Uses.**—See Neostigmine. Neostigmine bromide is used for the oral treatment of myasthenia gravis. The bromide is used in the oral tablet form as it is comparatively non-hygroscopic.

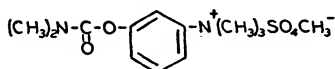
**Dosage.**—15 mg., three times daily. If necessary, the dose may be cautiously increased to 30 mg. three times daily.

HOFFMANN-LAROCHE, INC.

Tablets Prostigmin Bromide: 0.015 Gm.

U. S. patent 1,905,990 (April 25, 1933; expires 1950). U. S. trademark 293,889.

**NEOSTIGMINE METHYLSULFATE-U. S. P.—Prostigmin Methylsulfate-Hoffmann-LaRoche.**—"When dried at 100 C. for 3 hours, contains not less than 98 per cent of  $C_{13}H_{22}N_2O_6S$ ." U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Neostigmine Methylsulfate and Neostigmine Methylsulfate Injection.

**Actions and Uses.**—See Neostigmine.

**Dosage.**—Prevention of postoperative distention: small doses of the 1:4,000 solution are administered subcutaneously or intra-

muscularly at frequent intervals. Injections are begun twenty-four hours before the operation if feasible, otherwise as soon as possible, and repeated in 1 cc. doses every four to six hours until the second or third postoperative day. Treatment of post-operative distention: usually one or two ampuls of the 1:2,000 solution, as required, are administered subcutaneously or intramuscularly. Experimental use in the treatment of myasthenia gravis: only one ampul of the 1:2,000 solution is administered initially, the size and interval of the subsequent doses to be given as indicated by the degree and duration of the response to the initial dose. The course of treatment usually consists of from one to four ampuls (from 0.5 to 2 mg. of neostigmine methylsulfate).

HOFFMANN-LAROCHE, INC.

**Solution Prostigmin Methylsulfate 1:2,000 and 1:4,000:**  
1 cc. ampuls.

U. S. patent 1,905,990 (April 25, 1933; expires 1950). U. S. trademark 293,889.

### Anti-Parasympathomimetic Agents

An anti-parasympathomimetic (parasympatholytic) agent is a drug whose effects on the body resemble the effects of cutting the parasympathetic (craniosacral) nerve supply to various parts. The most familiar example is the effect of atropine on the heart, an effect which, with proper dosage, is much like that of cutting both vagus nerves and usually amounts to an acceleration. The dilation of the pupil and paralysis of accommodation by atropine are similar to the effects of cutting the oculomotor nerve. Typical antiparasympathomimetic drugs will also reduce gastrointestinal secretion and motility.

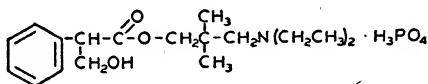
Atropine, the most typical of this class of drugs, is a rather specific antagonist to acetylcholine. It has, however, numerous side-effects which indicate that this antagonism is not its only mode of action, and the various other drugs classed with it here similarly have their individual peculiarities.

## ATROPINE DERIVATIVES AND ANALOGUES

### Synthetic Mydriatics

The usefulness of atropine is somewhat diminished by the fact that it affects, simultaneously, so many organs; on the eye its effects continue much longer than is in many cases desirable. Many attempts have been made to secure drugs of the atropine type with more specific actions or drugs that have a more transitory effect upon the eye. One of these drugs (homatropine) is a synthetic alkaloid analogous to atropine, the only difference being that it contains mandelic acid instead of tropic acid in combination with tropine; eucatropine is a combination of mandelic acid and a base similar to that contained in beta-eucaine.

**AMPROTROPINE PHOSPHATE**—Syntropan-Hoffmann-LaRoche.—The phosphate of the *dl*-tropic acid ester of 3-diethylamino-2,2-dimethyl-1-propanol. The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—The actions of amprotropine phosphate are similar to those of atropine. However, amprotropine phosphate acts to a certain extent directly on smooth muscle in addition to its inhibitory effect on parasympathetic endings. It does not depress salivary secretion as actively as atropine or induce mydriasis as readily, and its inhibitory action on the parasympathetic innervation of the heart is not as pronounced as that of atropine. Amprotropine phosphate is employed for its antispasmodic action on smooth muscle in Parkinson's disease (paralysis agitans), in seasickness and as a mydriatic for diagnosis.

*Dosage.*—For oral administration, one tablet (50 to 100 mg.) three or four times a day. In some cases of Parkinson's disease (paralysis agitans) as much as 2400 mg. in divided doses has been given within 24 hours without serious toxic symptoms. For subcutaneous or intramuscular administration, 1 cc. of amprotropine phosphate solution (representing 10 mg. of amprotropine phosphate) three times a day.

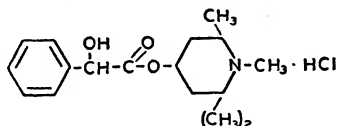
HOFFMANN-LAROCHE, INC.

**Syntropan (Powder):** 5 Gm. vials.

**Tablets Syntropan:** 50 mg. and 0.1 Gm.

U. S. patents 1,932,341 (Oct. 24, 1933; expires 1950) and 1,987,546 (Jan. 8, 1935; expires 1952). U. S. trademark 308,080.

**EUCATROPINE HYDROCHLORIDE**—U. S. P.—Euphthalmine Hydrochloride-Schering & Glatz, Division of Wm. R. Warner & Co., Inc.—“When dried over sulfuric acid for 4 hours, contains not less than 86 per cent and not more than 89 per cent of eucatropine ( $\text{C}_{17}\text{H}_{25}\text{O}_3\text{N}$ ).” U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Eucatropine Hydrochloride.

**Actions and Uses.**—Eucatropine hydrochloride produces prompt mydriasis free from anesthetic action, pain, corneal irritation or, in normal individuals, increase in intra-ocular tension. It should be noted, however, that eucatropine hydrochloride shares with other mydriatics the hazard of precipitating glaucoma in anatomically predisposed individuals. It has little or no effect on accommodation, and such effect as it has disappears more rapidly than that of atropine, cocaine, homatropine, etc. In its effects on the general system, eucatropine hydrochloride, very closely resembles atropine. It is useful as an aid in ophthalmoscopic examination in place of atropine, homatropine, etc.

**Dosage.**—From 2 to 3 drops of a 5 or 10 per cent solution and instilled into the eye at two 5 minute intervals, according to the age of the patient and the nature of the case.

SCHERING & GLATZ, DIVISION OF WM. R. WARNER & CO., INC.

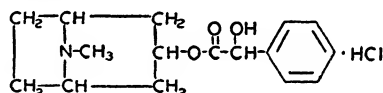
**Euphthalmine Hydrochloride (Powder):** 0.5 Gm. and 1 Gm.

U. S. patent 663,754 (expired). U. S. trademark 35,541.

WERNER DRUG & CHEMICAL CO.

**Eucatropine Hydrochloride (Powder):** bulk, 0.5 Gm., 1 Gm., 5 Gm. and 30 Gm.

**HOMATROPINE HYDROCHLORIDE.**—The hydrochloride of the alkaloid homatropine, obtained by the condensation of tropine and mandelic acid. The structural formula of homatropine hydrochloride may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Homatropine hydrochloride is useful when a paralysis of accommodation is necessary. Recovery from this cycloplegic effect is complete in one day, and is more rapid than in the case of any other of the atropine alkaloids exhibiting this action. Extreme care must be observed in its use with individuals disposed to glaucoma, but if cycloplegia is necessary its briefer action would cause it to be preferred. Homatropine dilates the conjunctival vessels and on injection lowers the blood pressure but affects the parasympathetic system, for instance the vagus, much less than atropine; five to ten times as high a dosage is necessary to paralyze.

**Dosage.**—It is applied to the eye in 1 per cent solution.

MERCK & CO., INC.

**Homatropine Hydrochloride (Crystals):** bulk.





MERCK & Co., INC.

**Scopolamine Hydrobromide (Crystals):** 65 mg., 0.3 Gm. and 1 Gm. vials.

**Scopolamine Hydrobromide (Powder):** 65 mg., 0.3 Gm. and 1 Gm. vials.

**SCOPOLAMINE STABLE-Hoffmann-LaRoche.**—Scopolamannit.—An aqueous solution of pure scopolamine hydrobromide, protected against decomposition by the addition of 10 per cent of mannite.

For tests and standards, see Section B.

*Actions, Uses and Dosage.*—The same as those of scopolamine hydrobromide-U. S. P.

HOFFMANN-LAROCHE, INC.

**Solution Scopolamine (Stable):** 0.3 mg. in 1 cc. and 0.6 mg. in 1 cc. ampuls. Each cubic centimeter contains 0.3 mg. of scopolamine hydrobromide in a 10 per cent aqueous solution of mannite.

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## CHAPTER IX

# Cardiovascular Agents

Cardiovascular agents comprise those drugs whose action upon the heart and other muscular portions of the vascular system is such as to affect either the total output of the heart or the distribution of blood to particular branches of the circulation. Accordingly, this chapter deals with (1) digitalis and other drugs which primarily affect the rhythm and output of the heart, and (2) vasodilator agents such as the nitrites.

The vasoconstrictor agents, such as epinephrine, will be found in the chapter on Autonomic Drugs, while ergot preparations are described in the chapter on Oxytocics. A number of drugs with less definite vasodilator effects are described in other chapters. Stimulants. Ethyl alcohol, sometimes employed internally in the form of "spirits" for its vasodilating action, is more reliable as a beverage than as a medicinal agent.

### Digitalis and Digitalis-like Principles and Preparations

The digitalis group embraces many crude drugs and proximate principles which have a peculiar action on cardiac muscle. Digitalis, strophanthus and squill have been investigated far more than the others, and we are much better informed concerning their actions; from them are derived nearly all the active principles and proprietary preparations of the group which have been included in N. N. R.

Digitalis and digitalis-like principles may be administered by mouth, by injection and as described under the accepted preparations. The U. S. Pharmacopeia recognizes a solution of digitalis for injections, but it should be remembered that the optimum frequency of repetition of the intravenous dose of different digitalis preparations varies widely, even with those of equal potency, depending on several factors, especially on difference in persistence of action. The physician must learn the proper intravenous dosage of any preparation of digitalis which he employs.

*Cardiac Action.*—The cardiac action of the individual drugs of the group is similar. They all act directly on heart muscle. They diminish the size of the heart as measured by the x-ray silhouette. While they increase the output of diseased hearts, they diminish that of normal hearts. The margin between therapeutic and toxic actions on the heart is believed by some to differ for different substances, although the weight of evidence indicates that the margin of safety does not differ. In patients

with auricular fibrillation they all slow the heart rate by a combination of a direct action on the heart muscle and an indirect vagal action. The larger the dose, the more pronounced the direct action. The proportion of these two actions is similar for the different members of the whole group.

Differences exist chiefly in relation to their absorption from the gastrointestinal tract, their speed of elimination, and their local emetic action. Their potencies differ, and difficulties arise from faulty standardization.

*Standardization.*—There are various methods for the standardization of this group of drugs, involving the use of several species of animals, the frog, the guinea pig, etc. The U. S. Pharmacopeia requires that digitalis be standardized against the U. S. P. Digitalis Reference Standard by the official cat method which involves intravenous injection into cats until death occurs by cardiac arrest. The available evidence indicates that the cat method yields results more nearly applicable to man than those of the frog method. The Standard preparation and the unknown are similarly injected into groups of animals and the average fatal doses of the two are compared. The unknown is then adjusted so that 0.1 Gm. has the potency of 0.1 Gm. of the Standard, or 1 U. S. P. Digitalis Unit. Since the U. S. P. Digitalis Unit is the result of an assay by the cat method and represents an improved technic in bioassay, the expression of potency in U. S. P. Digitalis Units is preferable to the older expression in terms of "cat units." By direct testing it has been found that 1 U. S. P. Digitalis Unit is equivalent approximately to 1.3 "cat units," using the cat method technique of the Pharmacopeia.

In the case of digitalis leaf and the tincture, the results of comparison by means of the cat method agree fairly satisfactorily with similar comparisons in humans to whom the drugs are given by oral administration, but there is less agreement in the case of purified materials because of wide differences in their absorption from the gastrointestinal tract, and the intravenous method does not distinguish absorbable from nonabsorbable material. Hence a U. S. P. Unit of different specimens of the Digitalis Leaf or Tincture Digitalis may be counted upon to produce substantially similar results when given orally to man (although there are some exceptions), but not so in the case of purified materials.

*Differences in Emetic Action.*—The digitalis principles are irritant to mucous membranes and subcutaneous tissues. When given in large doses, the local irritation in the gastro-intestinal tract may be sufficient to cause nausea and vomiting within several minutes to an hour or two. These drugs, however, are rarely administered in such doses, and when given in the usual smaller doses the local irritant action is insufficient to cause nausea or vomiting. The nausea or vomiting which follows the customary doses of digitalis is due to a systemic action after absorption and represents a toxic symptom. The seat of this

action is the vomiting center which is affected indirectly through the heart. The emetic action is roughly proportional to the cardiac effects of the various members of the group and when this undesired action is induced, it cannot be avoided by changing the mode of administration or by resorting to other members of the group. In such a case, the patient is overdigitalized and there is need for reducing the size of the dose.

*Differences in Absorption.*—Digitalis contains a mixture of glycosides, some of which are rapidly, and others poorly absorbed from the gastrointestinal tract. After an oral dose only about one fifth of the potent materials produce a systemic action, as shown by the fact that it requires only about one-fifth as much for intravenous as for oral administration to produce the same results. Digitoxin is almost completely absorbed, whereas other fractions may not be absorbed at all. The potent principles of strophanthus are so poorly absorbed from the gastrointestinal tract that they are undesirable for oral administration and are used chiefly by intramuscular or intravenous injection in small doses.

*Differences in Cumulative Action.*—All the digitalis bodies in common use are cumulative. Not all show the same degree of cumulation, however, due to the fact that some are more rapidly eliminated than others. The cumulative action is especially pronounced in the case of digitalis leaf and digitoxin. It is much less in the case of strophanthus and strophanthin.

*Intravenous Use.*—The frequency of repetition of the intravenous dose of different digitalis preparations varies widely, even with those of equal potency, depending on several factors, especially on difference in persistence of action. The physician must learn the proper intravenous dose of any preparation of digitalis which he employs.

### *Digitalis Principles and Preparations*

The disadvantages of all the drugs of the digitalis group have served as a constant stimulus in the search for pure principles suitable for intramuscular or intravenous administration. Pure principles would obviate the necessity of biological standardization. A potent pure principle which is completely absorbed from the gastrointestinal tract would make it possible to digitalize rapidly by oral administration without the danger of local irritant action of the large amount of nonabsorbable glycosides. Several glycosides are available in a fairly high degree of purity, such as strophanthin, ouabain, digitoxin. Many preparations, however, are mixtures of glycosidal materials such as Digifolin or Digalen.

*Proprietary Digitalis Preparations.*—Several digitalis preparations have been introduced into therapeutic use with the claim that they are composed either of pure principles, or of purified extracts of digitalis, and that they are devoid of certain disadvantages possessed by the preparations of the U. S. Phar-

macopeia. The Council urges on clinicians the necessity of acquiring skill in the use of digitalis materials by the careful observation of a very few members of the group, rather than to try to use without discrimination the large number of preparations which are offered.

**DIGALEN-Hoffmann-LaRoche.**—The cardioactive principles of digitalis as isolated by Cloetta. It is standardized by a modification of the intravenous cat method of Hatcher and Brody.

For tests and standards, see Section B.

*Actions and Uses.*—The same as those of digitalis.

*Dosage.*—The average maintenance dose of digalen (in 30 cc. vials) is from 1 to 2 cc. (0.8 to 1.6 U. S. P. unit). The maximum daily dosage is 6 cc. The average dose of tablets digalen is from 0.4 U. S. P. to 0.8 U. S. P. unit three times daily. The average dose of Digalen injectable is 2 cc.

*Preparation.*—

The dried and finely powdered leaves of digitalis are extracted with diluted alcohol; then the extract is mixed with lead acetate solution in order to remove chlorophyll and resins, and filtered. From this filtrate the excess of lead is precipitated with sodium sulfate, and the alcohol distilled off *in vacuo*. From the remaining aqueous solution, the active derivative of digitalis contained in digalen is extracted by ethereal solvents and precipitated afterward in an amorphous condition according to a special secret method. The several dosage forms are standardized by the intravenous cat method.

HOFFMANN-LA ROCHE, INC.

**Solution Digalen Injectable:** 2 cc. ampuls. Each 2 cc. represents 1 cat unit, in 8 per cent alcohol, equivalent in potency to approximately 81 mg. U. S. P. Digitalis Reference Standard = 0.8 U. S. P. Digitalis Unit.

**Solution Digalen:** 30 cc. vials. Each 1 cc. represents 1 cat unit, in 26 per cent alcohol, equivalent in potency to approximately 81 mg. U. S. P. Digitalis Reference Standard = 0.8 U. S. P. Digitalis Unit.

**Tablets Digalen:**  $\frac{1}{2}$  cat unit and 1 cat unit, respectively, equivalent in potency to 40 mg. U. S. P. Digitalis Reference Standard = 0.4 U. S. P. Digitalis Unit, and 81 mg. U. S. P. Digitalis Reference Standard (1942) = 0.8 U. S. P. Digitalis Unit.

U. S. trademarks 43,593 and 83,738.

**DIGIFOLIN-Ciba.**—A digitalis preparation containing the therapeutically desirable constituents of digitalis leaf. It is standardized by the U. S. P. Digitalis assay method.

For tests and standards, see Section B.

*Actions and Uses.*—The same as those of digitalis.

*Dosage.*—In the majority of cases in which digitalis therapy is indicated, the oral administration of 0.8 U. S. P. units in the

form of tablets or of Digifolin oral solution four times daily until the desired therapeutic effects or minor toxic symptoms appear.

Attention is called to the fact that oral Digifolin preparations provide the active glycosides in a form more readily absorbable than do the whole leaf preparations. This difference in absorption is responsible for a 20-30 per cent greater clinical effect from Digifolin as compared with crude digitalis preparations of equal unitage. Digifolin administered orally will, therefore, be found more active than indicated by the potency value obtained by the U. S. P. Cat Assay Method. However, as far as the Digifolin ampul solution for intravenous injection is concerned, the experimentally established potency will hold true under clinical conditions also.

*Preparation.—*

Dried and finely ground digitalis leaves are extracted with distilled water. The neutralized filtrate is then treated with alcohol, precipitated with a solution of lead acetate and filtered. The filtrate, after the removal of the lead and neutralization, is filtered and concentrated to a certain volume in a high vacuum at a temperature not exceeding 30 C. The active principles which separate through the foregoing concentration are collected and dried under a high vacuum at a temperature of 40 C. It is then dissolved in methyl alcohol, the filtrate treated with chloroform and the chloroform separated from the aqueous solution, distilled off and the residue dissolved in methyl alcohol. The aqueous solution which has been separated from the chloroform solution is treated with a mixture of ether two parts and benzene one part: the ether-benzene extract is concentrated under high vacuum at low temperature and the remaining residue dissolved in methyl alcohol. The several methyl alcohol solutions are mixed, decolorized with charcoal and concentrated under a high vacuum to a dry residue, which constitutes digifolin.

**CIBA PHARMACEUTICAL PRODUCTS, INC.**

**Solution Digifolin:** 2 cc. ampuls. Each 2 cc. contains digifolin equivalent to 0.1 Gm., one U. S. P. unit of digitalis leaves. The solution contains neither alcohol nor glycerin.

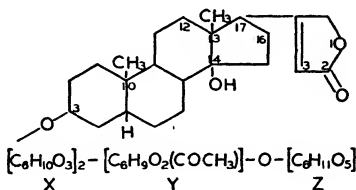
**Digifolin (Liquid):** Each 1 cc. contains digifolin equivalent to 0.1 Gm., one U. S. P. unit of digitalis leaves. It contains 12 per cent alcohol.

**Tablets Digifolin:** Each tablet contains digifolin equivalent to 0.1 Gm., one U. S. P. unit of digitalis leaves.

U. S. trademark 448,819.

**DIGILANID-Sandoz.** — A mixture of the isomorphous crystallized cardio-active glycosides lanatoside-A ( $C_{49}H_{76}O_{19}$ ), lanatoside-B ( $C_{49}H_{76}O_{20}$ ), and lanatoside-C ( $C_{49}H_{76}O_{20}$ ), obtained from the leaves of *Digitalis lanata*. The three components are present in the mixture in the proportions in which they occur in the crude drug, namely about 47 per cent lanatoside-A, 16 per cent lanatoside-B and 37 per cent lanatoside-C. The structural formula of lanatoside-A, as far as it is known, is represented here. In this formula X = digitoxose, Y = acetyldigitoxose and Z = glucose. Lanatoside-B and lanatoside-C differ from

lanatoside-A in having a hydroxyl group attached to carbon atoms 16 and 12 respectively.



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses are closely similar to those of digitalis U. S. P.

**Dosage.**—The average oral daily dose is from 1.6 to 3.2 U. S. P. units in the form of tablets or from 1 to 2 U. S. P. units as the liquid until the therapeutic effects are induced or until minor toxic symptoms appear, after which a maintenance dose of about half that just given will usually be sufficient. Urgent cases sometimes require the administration of larger oral doses or the intramuscular or intravenous injection of suitable doses. These demand the careful observation of the proper technic.

**Preparation.**—

The dry leaves of *Digitalis lanata* are ground with ammonium sulfate, wet with water and extracted with ethyl acetate. The filtered extract is evaporated to dryness *in vacuo*, treated with ether and allowed to stand until the mass becomes solid. The ether is poured off and the residue digested with ether. The dried residue from the operation is pulverized, dissolved in methyl alcohol and treated with lead hydroxide in water. The resultant mixture is neutralized and filtered; the filtrate is concentrated *in vacuo* and the precipitated glucosidal mixture filtered. The residue is recrystallized from methyl alcohol and water mixtures.

Digilanid crystallizes from aqueous methanol solutions in flat prisms which contain 6 per cent (2 mol.) of methanol and 3.5 per cent (2 mol.) of water as solvents of crystallization. When dried in a high vacuum at 90 C., these solvents are lost. On standing, the dried material takes up approximately 7 per cent of moisture; the dosage of the product is based on this hydrated form.

SANDOZ CHEMICAL WORKS, INC.

**Solution Digilanid:** 2 cc. ampuls. (For Intramuscular or Intravenous Use.) Each ampul contains 0.4 mg. of Digilanid, equivalent to 1 U. S. P. unit of digitalis. Alcohol 7.5 per cent by weight. Glycerin 15 per cent by weight.

**Solution Digilanid:** 4 cc. ampuls. (For Intravenous or Intramuscular Use.) Each ampul contains 0.8 mg. of Digilanid, equivalent to 1.8 U. S. P. units of digitalis. Alcohol 7.5 per cent by weight. Glycerin 15 per cent by weight.

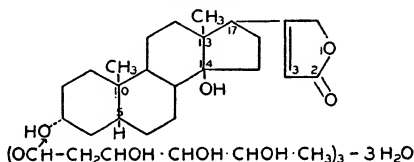
**Solution Digilanid:** 30 cc. vials. Each 1 cc. contains 0.33 mg. of Digilanid, equivalent to 0.8 U. S. P. unit of digitalis. Alcohol 28 per cent by weight. Glycerin 10 per cent by weight.

**Suppositories Digilanid:** 0.5 mg. (1.2 U. S. P. units).

**Tablets Digilanid:** 0.33 mg. (0.8 U. S. P. unit).

U. S. patents 1,923,490 (Feb. 19, 1931; expires 1948) and 1,923,491 (Aug. 22, 1931; expires 1948). U. S. trademark 291,301.

**DIGITOXIN-U. S. P.**—**Digitaline Nativelle-Varick.**—"Digitoxin is either pure digitoxin ( $C_{41}H_{64}O_{13}$ ) or a mixture of cardioactive glycosides obtained from *Digitalis purpurea* Linné (Fam. *Scrophulariaceae*) and consisting chiefly of digitoxin. The potency of digitoxin, assayed biologically, corresponds to the potency of an equal weight of U. S. P. Digitoxin Reference Standards." U. S. P. The structural formula for digitoxin, as far as it is known, may be represented as shown below, where the sugar residue shown attached at position 3 is digitoxose.



For description and standards see the U. S. Pharmacopeia under Digitoxin, Digitoxin Injection and Digitoxin Tablets.

**Actions and Uses.**—Digitoxin, the chief active glycoside of *Digitalis purpurea* was used by Nativelle in 1868 and first reported in the literature in 1869. It is available in crystalline form, sufficiently pure to be administered by weight. It is almost completely absorbed from the intestinal tract and a given dose produces practically the same therapeutic effect whether given by mouth or by vein. Nausea or vomiting due to local action are almost never encountered. In oral administration, 1 mg. of digitoxin exerts approximately the same therapeutic action as one gram of U. S. P. XIII Digitalis. The full digitalizing effect of the drug following oral administration is obtained about as quickly as when the same dose is administered intravenously, and thus the drug does not need to be administered intravenously in the average patient, but may be given by vein to comatose patients and to patients who cannot take oral medication for other reasons.

**Dosage.**—Most patients can be digitalized by the administration of not more than 1.2 mg., although a few may require a larger amount, while others will show some sign of intoxication from even this quantity. For patients who have received no digitalis in any form for at least two weeks, the average dose of 1.2 mg. may be given at one time, but under most conditions it is wiser to begin with 0.6 mg., administering subsequent doses of 0.4 mg. down to 0.2 mg. on the same day, then following with a daily maintenance dose; such maintenance may usually be accomplished by giving daily doses of 0.2 mg. Digitalization



may also be accomplished by administering each day a dose of 0.2 mg. for a period of one to three weeks even when no larger initial dose has been given.

*Caution.—Digitoxin is extremely poisonous.*

THE CENTRAL PHARMACAL COMPANY

Tablets Digitoxin: 0.2 mg.

MCNEIL LABORATORIES, INC.

Solution Digitoxin: 0.2 mg. per cc., 1 cc. ampuls.

THE WM. S. MERRELL Co.

Tablets Unidigin: 0.2 mg., digitoxin, U. S. P.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Digitoxin: 0.1 mg. and 0.2 mg.

R. J. STRASENBURGH Co.

Tablets Digitoxin: 0.1 mg., and 0.2 mg.

VARICK PHARMACAL Co., INC.

Solution Digitaline Nativelle: 1 cc. Ampuls (0.2 mg.) and 2 cc. Ampuls (0.4 mg.).

Tablets Digitaline Nativelle: 0.1 mg. and 0.2 mg.

WYETH INCORPORATED

Solution Purodigin: 1 cc. ampuls and 1 cc. Tubex (U. S. trademark 406,632). Each cubic centimeter contains 0.2 mg. of digitoxin in 40 per cent alcohol solution.

Tablets Purodigin: 0.1 mg. and 0.2 mg.

U. S. trademark 411,271.

**DIGITAN-Merck.**—A purified extract of digitalis containing the active principles in the same proportions as they exist in the whole leaf. In Digitan, 85 per cent of the inactive substances present in the ordinary extract have been removed and it is free from digitonin. Digitan is physiologically standardized according to the official U. S. P. procedure.

For tests and standards, see Section B.

*Actions and Uses.*—The same as those of digitalis.

*Dosage.*—The same as that of digitalis.

*Preparation.*—

Digitan is obtained by removing objectionable constituents from an alcoholic extract of digitalis, neutralized with alkaline hydroxides, by the addition of ether, petroleum benzine or some other suitable precipitant, and reducing the purified liquid to a powder by evaporating with milk sugar.

MERCK & Co., INC.

Digitan Powder.

**Solution Digitan:** 1 cc. ampuls. A sterilized solution of Digitan, 0.1 Gm. per cubic centimeter.

**Tablets Digitan:** 0.1 Gm.

U. S. patent 943,578 (Dec. 14, 1909; expired). U. S. trademark 138,484.

**DIGITOL-Sharp & Dohme.**—Tincture of Digitalis (Fat-Free).—A biologically standardized, fat-free tincture of digitalis, corresponding in drug strength to tincture of digitalis-U. S. P., and containing 73 per cent alcohol.

**Actions and Uses.**—The same as those of digitalis. Digitol was introduced at a time when the "fat" of digitalis was believed to cause gastric disturbances. At present the claim of superiority on this basis is not tenable. The only advantage of the defatting process is to make possible a nearly clear mixture of the product with water.

**Dosage.**—From 0.3 to 1 cc.

**Preparation.**—

Digitalis which has previously been subjected to percolation with petroleum benzine is extracted by percolation with hydro-alcoholic menstruum in the usual way.

Digitol is a brownish-green liquid having a characteristic and highly alcoholic odor and a bitter taste. Each cc. represents one U. S. P. Digitalis Unit.

SHARP & DOHME, INC.

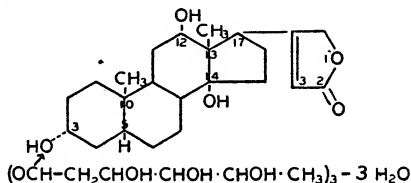
**Digitol (Liquid).**

U. S. trademark 208,315.

**DIGOXIN-U. S. P.**—"A glycoside which may be prepared from the leaves of *Digitalis lanata*, Ehrh. (Fam. *Scrophylariaceae*)." U. S. P.

The crude lanatosides from the leaves are separated by physical methods into lanatosides A, B and C. Digoxin is formed from lanatoside C by hydrolytic removal of acetyl and glucose groups. The potency of Digoxin, assayed biologically, corresponds to the potency of an equal weight of U. S. P. Digoxin Reference Standard.

The structural formula of digoxin, as far as it is known, may be represented as shown below, where the sugar attached at position 3 is digitoxose.



For description and standards see the U. S. Pharmacopeia under Digoxin, Digoxin Injection and Digoxin Tablets.

*Actions and Uses.*—The actions and uses are closely similar to those of digitalis-U. S. P. As a purified substance it is claimed to have particular usefulness when rapid digitalization is desired. Its action is manifest usually within a few hours when administered by mouth and within a few minutes when given intravenously.

*Dosage.*—Before administering a large dose of digoxin, it must be ascertained that no drug of the digitalis group has been given within two weeks.

For rapid digitalization by the oral route, an initial dose of approximately 0.75 mg. may be administered, followed by doses of 0.25 to 0.75 mg. at six hour intervals until the ventricular rate lies between 60 and 70, or the maximum therapeutic effect is obtained, or toxic symptoms appear.

Very rapid digitalization may be accomplished with an intravenous injection of 0.75 to 1.0 mg. Ventricular slowing usually begins within a few minutes and is maximal in one to two hours. If complete digitalization is not obtained after six hours, additional doses of 0.25 to 0.5 mg. of digoxin may be given intravenously at six hour intervals.

For maintenance 0.25 to 0.75 mg. may be given daily by mouth, or 0.25 to 0.5 mg. may be given intravenously.

Digoxin injection is a tissue irritant and the contents of the ampul should be diluted with 10 cc. of sterile isotonic solution. The product should be injected slowly (five to ten minutes) and care taken to avoid extravenous injection.

*"Caution—Digoxin is extremely poisonous." U. S. P.*

BURROUGHS WELLCOME & CO., INC.

**Tabloid Digoxin:** 0.25 mg.

**Solution Digoxin, 0.05%.** 1 cc. Contains 0.5 mg. of digoxin per cubic centimeter in 70 per cent alcohol solution.

**GITALIN (AMORPHOUS).**—A glycosidal constituent of *Digitalis purpurea* Linné prepared according to the method of Kraft.

For tests and standards, see Section B.

*Actions and Uses.*—The same as those of digitalis.

*Dosage.*—Full digitalis effects are usually obtained after a total dosage of 4 to 6.5 mg., or from five to eight tablets. These effects may be obtained by the administration of two to three tablets per day for three or four days. The same precautions should be taken with gitalin as with any digitalis preparation or digitaloid drug. Should toxic symptoms, such as nausea or vomiting, occur during the course of digitalization, administration of the drug should be discontinued. After the desired clinical effects have been induced, the patient may be placed on a maintenance dose of 0.25 mg. to 0.75 mg. (one-third to one tablet) daily. The amount varies according to the individual

requirements of the patient. Gitalin (amorphous) is less cumulative than digitoxin but more so than ouabain and most tinctures of digitalis. However, since gitalin is absorbed rapidly and much more completely from the gastro-intestinal tract than digitalis leaf, its potency is greater than indicated by its U. S. P. strength.

*Preparation.*—

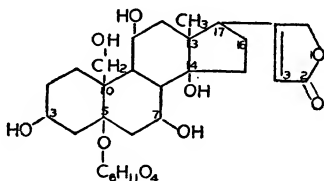
Dried and ground leaves of *Digitalis purpurea* Linné are extracted with cold, distilled water. This aqueous infusion is then treated with basic lead acetate and the lead subsequently removed by precipitation with sodium sulfate. The resulting filtrate is agitated with chloroform and allowed to separate. From the chloroform extract the gitalin (amorphous) substance is precipitated by means of petroleum ether. The precipitate is subjected to further purification and finally dried in vacuo. The entire process of extraction and purification is conducted without the aid of heat.

RARE CHEMICALS, INC.

**Tablets Gitalin (Amorphous):** 0.75 mg. Each tablet is scored into segments of 0.25 mg. for convenience in regulation of the daily maintenance dose.

*Related Digitalis Principles*

**OUABAIN-U. S. P.—G. Strophanthin.**—"A glycoside obtained from the seeds of *Strophanthus gratus* (Wall. et Hook.) Baillon (Fam. *Apocynaceae*). The potency of Ouabain, assayed biologically, corresponds to the potency of 91 per cent of an equal weight of U. S. P. Ouabain Reference Standard." U. S. P. The structural formula of ouabain, as far as it is known, may be represented as shown below, where the sugar attached at position 5 is rhamnose.



For description and standards see the U. S. Pharmacopeia under Ouabain and Ouabain Injection.

**Actions and Uses.**—The pharmacologic action of ouabain is probably qualitatively identical with that of the official strophanthus or strophanthin, but ouabain is more active than the official strophanthin when injected intramuscularly or intravenously. This action develops more rapidly, the drug is more quickly excreted, and shows less tendency to cumulative action than does digitalis.

Ouabain is used only for injection in place of strophanthus or strophanthin as a substitute for digitalis.

**Dosage.**—Ouabain is absorbed so slowly and so irregularly from the alimentary canal that the oral administration of the drug is not to be recommended and is even considered unsafe.

For intravenous or intramuscular administration, the dose is 0.5 mg. and this dose should not be repeated as a rule within less than 24 hours. It is best employed dissolved in from 4,000 to 8,000 parts of isotonic solution of sodium chloride. When the intramuscular or intravenous dose is to be repeated within less than 24 hours, a smaller amount should be administered.

Since ouabain solution may deteriorate rapidly, when sterilized in glass which yields traces of alkali, only solutions which have been kept in alkali-free glass containers should be used.

**Caution**—*Ouabain is extremely poisonous.*

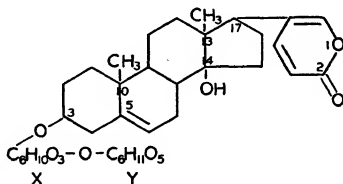
MERCK & Co., INC.

**Ouabain (G-Strophanthin) (Powder):**

CARROLL DUNHAM SMITH PHARMACAL COMPANY

**Solution Ouabain:** Ampuls 0.1 mg. in  $\frac{1}{2}$  cc. and 0.5 mg. in 2 cc.

**SCILLAREN-Sandoz.**—A mixture of the natural glycosides, scillaren-A and scillaren-B, occurring in fresh squill *Urginea maritima*, in the proportions in which they exist in the fresh crude drug; namely, about 2 parts of scillaren-A to 1 part of scillaren-B. Completely dried Scillaren contains approximately 98 per cent of the active glycosides. Scillaren dried in a high vacuum at 78 C. for 15 hours loses not more than 6 per cent of its weight. The structural formula of scillaren-A, as far as it is known, may be represented as shown below, where X = rhamnose and Y = glucose.



For tests and standards, see Section B.

**Actions and Uses.**—The cardiac action of Scillaren is essentially similar to that of digitalis, but this action is apparently less persistent than that of digitalis.

**Dosage.**—1.6 mg. orally from three to four times daily until compensation is established or until minor toxic symptoms are induced. After compensation is established, 0.8 mg. may be administered from two to four times daily.

SANDOZ CHEMICAL WORKS, INC.

**Tablets Scillaren:** 0.8 mg.

**Solution Scillaren:** Each cubic centimeter represents 0.8 mg. of Scillaren. Scillaren oral solution contains 25 per cent alcohol and 20 per cent glycerin by weight and the solution for injection 6 per cent alcohol and 15 per cent glycerin by weight.

U. S. patent No. 1,516,552 (Nov. 25, 1924; expired) and No. 1,579,338 (April 6, 1926; expired). U. S. trademark 173,046.

**Dosage.**—2 cc. (40 drops) three to four times daily; after compensation is established, 1 cc. (20 drops) two to four times daily. A dropping device is supplied with each package, designed to yield 20 drops per cubic centimeter.

**SCILLAREN-B-Sandoz.**—The amorphous component of the natural mixture of the glycosides occurring in squill, *Urginea maritima*. Completely dried Scillaren-B contains approximately 99.5 per cent active glycosidal substance. Scillaren-B dried in a high vacuum at 78 C. for 15 hours loses not more than 5 per cent of its weight.

For tests and standards, see Section B.

**Actions and Uses.**—The same as those of Scillaren.

**Dosage.**—Scillaren-B is for intravenous administration when immediate action is indicated. Not more than 0.5 mg. of Scillaren-B should be injected intravenously within 24 hours.

SANDOZ CHEMICAL WORKS, INC.

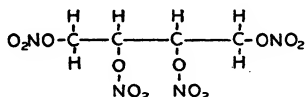
**Solution Scillaren-B:** 0.5 mg. in 1 cc. ampuls. Scillaren oral solution contains 25 per cent alcohol and 20 per cent glycerin by weight and the solution for injection 6 per cent alcohol and 15 per cent glycerin by weight.

U. S. patent 1,516,552 (Nov. 25, 1924; expired) and 1,579,339 (April 6, 1926; expired). U. S. trademark 173,046.

## Organic Nitrates

The esters of nitric acid and the higher alcohols (glycerin, propanetriol, erythrite, butanetetrol, etc.) have an action on the blood vessels similar to that of the inorganic nitrites (sodium nitrite) and that of the nitrous acid esters of the alcohols (amyl nitrite, ethyl nitrite). This is generally attributed to the formation in the body of nitrites from them.

**ERYTHRITYL TETRANITRATE TABLETS-U. S. P.**  
—Erythrol Tetranitrate Tablets.—Tetranitrol Tablets.—“Contain not less than 93 per cent and not more than 107 per cent of the labeled amount of erythrityl tetranitrate  $[C_4H_6(NO_3)_4]$ .”  
U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Erythrityl Tetranitrate Tablets.

**Actions and Uses.**—Erythrityl tetranitrate is a vasodilator like nitroglycerin. Its action is slower and more lasting, beginning in fifteen minutes and persisting for three or four hours.

The action of erythrityl tetranitrate is too slow to give satisfactory relief to acute attacks of angina pectoris. It is reported as useful as a prophylactic in preventing anginal pain if administered shortly before exercise, but when given routinely to prevent attacks the results of carefully controlled studies have been negative. Given at bedtime, it may have some value in those attacks which are prone to occur during the night in very severe cases of this disease.

Although erythrityl tetranitrate causes a prolonged fall of blood pressure in certain cases of hypertension, the reduced pressure cannot be maintained by repeated administration of this drug. This invalidates its use in the prolonged treatment of hypertension. Its efficacy in peripheral vascular disease is also questionable because the fall in blood pressure calls forth vasoconstrictor reflexes. These reflexes compete with the dilator influence of erythrityl tetranitrate and often overcome it resulting in peripheral vasoconstriction. This drug often causes severe headaches.

**Dosage.**—From 30 mg. to 60 mg. every four to six hours. Pure erythrityl tetranitrate is a crystalline mass, which explodes on percussion, hence it is marketed chiefly in the form of tablets. Sold in the form of tablets only.

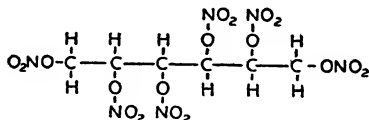
BURROUGHS WELLCOME & Co., INC.

**Tabloid Erythrityl Tetranitrate:** 16 mg. and 32 mg.

MERCK & Co., INC.

**Tablets Erythrol Tetranitrate:** 16 mg. and 32 mg.

**MANNITOL HEXANITRATE.**—An explosive compound formed by the nitration of mannitol, a sugar alcohol. Its stability at ordinary temperatures is such that it may be used commercially but it is distinctly less stable than nitroglycerin at 75 C. Its use for pharmaceutical preparations is only in admixture with carbohydrate substances in dilutions corresponding to 1 part of mannitol hexanitrate to 9 or more parts of carbohydrate. In such dilutions mannitol hexanitrate is nonexplosive. Mannitol hexanitrate has the following structural formula:



For tests and standards, see Section B.

**Actions and Uses.**—Mannitol hexanitrate exerts the vasodilator action of the nitrite ion ( $\text{NO}_2$ ), causing a relatively persistent relaxation of smooth muscle, especially that of the smaller blood vessels. This relaxation causes a fall in blood pressure, occurring within fifteen to thirty minutes and lasting four to six hours. It also relaxes the coronary vessels in experimental animals. The action is too slow to give effective relief to attacks of angina pectoris, and the evidence that it is useful in preventing attacks is not convincing. The drug does not benefit most cases of essential hypertension, as no permanent lowering of blood pressure can be perceived. It has no direct effect on the myocardium.

Toxic effects include the formation of methemoglobin (which should constitute a warning concerning the use of nitrites by anemic persons), rise in intraocular tension, headache, increase in intracranial pressure and cardiovascular collapse. Treatment of severe untoward effects includes cessation of therapy with the drug, administration of oxygen, transfusions for shock, removal of drug from the stomach and other supportive measures such as lowering of the head and elevation of the limbs.

**Dosage.**—Mannitol hexanitrate may be administered in 15 to 60 mg. doses at intervals of four to six hours. Occasionally this dose may be exceeded, but careful watch of the blood pressure and the patient should be kept at all times so that the development of undesirable side effects and the patient's tolerance may be noted. The dosage should be kept at a minimum compatible with satisfactory results. Patients with extensive arteriosclerosis may not present reductions in blood pressure and, as in other instances, if no reduction occurs, medication with mannitol hexanitrate should be discontinued.

**ABBOTT LABORATORIES**

**Tablets Mannitol Nitrate:** 16 mg. and 32 mg. Each tablet contains not less than 93 nor more than 107 per cent of the labeled amount of mannitol hexanitrate and also contains at least 9 parts of carbohydrate by weight.

**GEORGE A. BREON & Co., INC.**

**Tablets Mannitol Hexanitrate:** 30 mg.

**FLINT, EATON & Co.**

**Tablets Mannitol Hexanitrate:** 32 mg.

**THE NATIONAL DRUG Co.**

**Tablets Mannitol Hexanitrate:** 30 mg.

**WILLIAM H. RORER, INC.**

**Tablets Mannitol Hexanitrate:** 32 mg.

**THE SMITH-DORSEY COMPANY**

**Tablets Mannitol Hexanitrate:** 30 mg.





tients appear much more susceptible to its intoxication than others. The untoward symptoms brought about by its use in these patients are nausea, vomiting, convulsions, palpitation, headache, faintness and flushing. In most cases following the administration of the drug, the pulse increases in rapidity before the normal rhythm is established. In some cases the effect of the drug is restricted to this alteration of rhythm. In a few instances, such serious results as rapid idioventricular rhythms (ventricular tachycardia) have been initiated during the course of therapy. Toxic effects may appear after the establishment of a normal rhythm. Some cases have been reported in which sudden death occurred a short time after the drug had been stopped. The drug is rapidly eliminated.

**Dosage.**—Quinidine is generally administered as quinidine sulfate. Commonly 0.2 Gm. of quinidine sulfate is given as a preliminary dose and is repeated after two hours to determine the patient's susceptibility to the drug. If there are no symptoms following this preliminary dose, therapeutic administration is begun on the following day when from 0.2 Gm. to 0.4 Gm. is given from three to five times daily, for one to three days. As a rule, if the establishment of the normal rhythm can be effected, the change occurs after from one to three days' treatment. The maximum dose per day advised by most authors is from 1 to 2 Gm. In ventricular tachycardia following cardiac infarction, larger doses are sometimes required and are well tolerated. If toxic symptoms occur, the administration of the drug should be discontinued. Intravenous administration is dangerous and is not recommended.

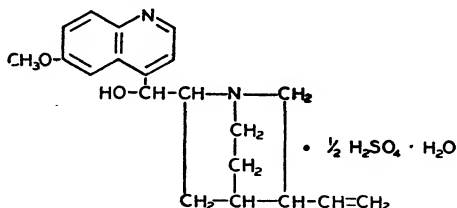
MALLINCKRODT CHEMICAL WORKS

**Quinidine (Powder):** bulk.

**MERCK & Co., INC.**

**Quinidine-N. F. V (Crystals or Powder):** bulk.

**QUINIDINE SULFATE-U. S. P.**—"The sulfate of an alkaloid obtained from the bark of the stem or of the root of various species of *Cinchona* and their hybrids and from *Remijia pedunculata* Flückiger (Fam. *Rubiaceae*)." U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Quinidine Sulfate and Quinidine Sulfate Tablets.

*Actions and Uses.*—See preceding article, Quinidine.

*Dosage.*—See preceding article, Quinidine. Quinidine sulfate may be administered in the form of cachets, capsules, pills or tablets.

ABBOTT LABORATORIES

**Capsules Quinidine Sulfate: 0.2 Gm.**

DAVIES, ROSE & COMPANY, LTD.

**Tablets Quinidine Sulfate: 0.2 Gm.**

MALLINCKRODT CHEMICAL WORKS

**Quinidine Sulfate (*Powder*): bulk.**

MERCK & Co., INC.

**Quinidine Sulfate (*Crystals*): bulk.**

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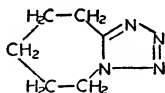
## CHAPTER X

# Central Nervous System Stimulants

This chapter describes a number of drugs that stimulate the brain and spinal cord. Injections of caffeine and sodium benzoate, for instance, and inhalations of carbon dioxide with air or oxygen are practically never given for any other purpose. Oxygen itself is not strictly a stimulant, but is included here for convenience. Picrotoxin has also been included because it is particularly valuable in combating the depression of severe barbiturate intoxication.

Certain autonomic drugs that produce conspicuous central stimulating effects are also included here. Theophylline ethylenediamine, which is useful on combating Cheyne-Stokes respiration because of its central stimulating action, is described with other theophylline and theobromine preparations in the chapter on Diuretics.

**METRAZOL**—Bilhuber-Knoll. — Pentamethylenetetrazol. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The action of metrazol is primarily stimulating to the midbrain, the medullary centers and perhaps the spinal cord. Its action following injection intravenously or subcutaneously is induced promptly. Although metrazol has been used to stimulate the vasomotor and respiratory centers, this action is observed clinically usually only when the dose approaches the convulsive level. Metrazol, like the other analeptics, is effective in accelerating recovery from narcotic depression, especially that produced by barbiturates. It has been used in the treatment of barbiturate poisoning with great benefit. The use of metrazol is reported as a sustaining agent and restorative in chronic, cardiac and circulatory insufficiency, in pneumonia, and in other infectious diseases, but there has been no convincing evidence of its value in these conditions. It has also been reported to be of value in emergencies due to cardio-

vascular collapse, again without valid evidence of its effectiveness.

Metrazol has come into extensive use in the treatment of mental disorders in doses which induce convulsions. For this purpose, it is safer than insulin hypoglycemia. Reports have appeared of minor fractures of the vertebrae, without paralysis, induced by these convulsions. These may be prevented by the cautious use of curare prior to the use of metrazol. Because of its difficulties and dangers, convulsive treatment should be instituted only by psychiatrists or in an institution where the necessary care can be given.

*Dosage.*—Intramuscularly, subcutaneously, or intravenously, from 0.1 to 0.3 Gm. repeated as required; orally, from 0.1 to 0.3 Gm. several times daily.

BILHUBER-KNOLL CORP.

**Solution Metrazol:** 1 cc. and 3 cc. ampuls. Each 1 cc. contains 0.1 Gm. of pentamethylenetetrazol in aqueous solution with 0.1 per cent sodium phosphate.

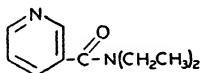
**Solution Metrazol 10%:** 30 cc. bottles. An aqueous solution containing pentamethylenetetrazol, 0.1 Gm. per 1 cc. for oral use.

**Solution Metrazol 10%:** 30 cc. bottles. A sterile solution containing pentamethylenetetrazol 0.1 Gm. per cubic centimeter, for parenteral administration.

**Tablets Metrazol:** 0.1 Gm.

U. S. patent 1,599,493 (Sept. 14, 1926; expired). U. S. trademark 249,687.

**NIKETHAMIDE.**—N,N-Diethylpyridine-3-carboxamide.—N,N-diethyl nicotinamide. The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Experiments involving several species of animals indicate that the action of nikethamide is mainly on the central nervous system. In animals the drug appears to stimulate medullary centers, giving rise to an increased rate and depth of respiration and to peripheral vasoconstriction. In animals its administration usually results in some increase in blood pressure, but this may be preceded by a temporary and sudden lowering of the pressure. Claims have been made for the use of nikethamide as an agent to raise blood pressure in human beings, but the results are not consistent; apparently the vasomotor center can be stimulated only under certain circumstances.

It has been suggested that any rise in blood pressure may be secondary to improved respiration and to stimulation of the reflex centers. Small doses in experimental animals exert no action on the coronary vessels, but larger doses may increase the coronary flow. However, clinical evidence for the use of nikethamide to promote increased coronary blood flow is not conclusive.

Nikethamide has been used clinically as a cardiac stimulant, but the majority of published reports do not reveal it to be especially efficient and it is probable that the cardiac effect does not depend on a direct action on the myocardium. Most experiments with carefully adjusted doses show no consistent increase in the amplitude of the heart beat, and any beneficial effect in cases associated with imperfect filling of the right side of the heart may be due to a respiratory effect leading to an increased oxygen exchange in the lung. The relief of respiratory distress in cardiac disease, as in paroxysmal dyspnea, may result from the effect on the respiratory system. At the present time there is no justification for the use of nikethamide in association with chronic myocardial failure, myocarditis, coronary disease (coronary thrombosis or coronary sclerosis) and angina pectoris. The analeptic action of nikethamide suggests its usefulness in combating acute respiratory depression from anesthetics, alcoholic intoxication and hypnotics. However, it is not clear that nikethamide is superior in this respect to other available drugs, especially in cases of barbiturate poisoning. Because of its additional action on peripheral vascular tone it appears to be of benefit in cases of acute circulatory failure occurring during the course of surgical procedures or pneumonia. However, nikethamide is contraindicated in pneumonia unless circulatory collapse supervenes.

*Dosage.*—Nikethamide, a liquid, is available as an aqueous solution, 25 per cent W/V, for oral and for subcutaneous, intramuscular or intravenous administration, but in emergencies no benefit can be expected from oral administration nor, usually from subcutaneous administration. The drug should preferably be given intravenously. Because nikethamide, after intravenous administration, is rapidly inactivated, the dose depends on the rate of injection. When doses larger than 3 cc. are given, the administration should be slow and the general reaction of the patient should be watched. It should be remembered that large or toxic doses produce convulsions and may cause death from respiratory failure. The dose may be repeated at intervals according to the needs of the patient.

#### ABBOTT LABORATORIES

**Solution Nikethamide 25% W/V: 1.5 cc. ampul.**

#### GEORGE A. BREON & COMPANY, INC.

**Solution Nikethamide 25% W/V: For oral use 15 cc., 88.7 cc. and 480 cc. bottles.**

**Solution Nikethamide 25% W/V:** 1½ cc. ampuls.

BUFFINGTON'S, INC.

**Solution Nikethamide 25% W/V:** 2 cc. and 5 cc. ampuloids.

THE DRUG PRODUCTS Co., INC.

**Solution of Nikethamide 25% W/V:** 1.5 cc. ampuls; 30 cc. vials with chlorobutanol 0.5 per cent added as a preservative.

ENDO PRODUCTS, INC.

**Solution Nikethamide 25% W/V:** 1.5 and 5 cc. ampuls and for oral administration 15 cc. vials.

FLINT, EATON & COMPANY

**Solution Nikethamide 25% W/V:** 2 cc. ampuls.

LAKESIDE LABORATORIES, INC.

**Solution of Nikethamide 25% W/V:** 1.5 cc. ampuls with 0.5 per cent chlorobutanol added as a preservative; 15 cc. vial preserved with chlorobutanol 0.5 per cent.

THE NATIONAL DRUG Co.

**Solution Nikethamide 25%:** 5 cc. ampuls and for oral use 15 cc. and 120 cc. bottles with 0.5 per cent chlorobutanol added as a preservative.

PREMO PHARMACEUTICAL LABORATORIES

**Solution Nikethamide 25% W/V:** For oral use 15 cc., 45 cc. and 480 cc. bottles. For parenteral use 1.5 cc. and 5 cc. ampuls.

CARROLL DUNHAM SMITH PHARMACAL Co.

**Solution Nikethamide 25% W/V:** 15 cc. vials.

SMITH-DORSEY COMPANY

**Solution Nikethamide 25% W/V:** 1.5 cc. and 5 cc. ampuls.

THE UPJOHN COMPANY

**Solution Nikethamide 25% W/V:** 1.5 cc. and 10 cc. ampuls and 88.7 cc. bottles.

WM. R. WARNER & Co., INC.

**Solution Nikethamide 25% W/V:** 2 cc. and 5 cc. ampuls.

**PICROTOXIN-U. S. P.**—"An active principle obtained from the seed of *Anamirta Cocculus* (Linné) Wight et Arnott (Fam. *Menispermaceae*)."  
U. S. P.

For description and standards see the U. S. Pharmacopeia under Picrotoxin and Picrotoxin Injection.

*Actions and Uses.*—Picrotoxin is a stimulant and convulsant acting chiefly on the higher centers. Thus if the midbrain and pons are removed in mammals, the convulsive action disappears,

although signs of medullary stimulation may persist. Aside from the convulsions which picrotoxin produces, the principal important actions are those relating to medullary stimulation. Acceleration of the respiratory rate, rise in blood pressure, slow pulse and nausea and vomiting are the usual effects observed after the administration of picrotoxin.

The principal use of picrotoxin is in the treatment of severe barbiturate poisoning as shown by the general discussion of reflex activity. The drug has a special analeptic action against the narcosis induced by overdosage of the barbiturates; it will overcome the depression of respiration and increase the oxygen consumption of the poisoned animal. The period of narcosis is appreciably shortened. Although highly poisonous to normal persons, the toxicity of picrotoxin appears to be less in persons narcotized by the barbiturates. The drug is rapidly destroyed in the body.

*Dosage.*—In cases of barbiturate poisoning, 6 mg. should be administered intravenously and should be increased by 3 mg. at 15 minute intervals up to a total of 15 mg. until the desired response is obtained. Artificial respiration, an open airway, oxygen, gastric lavage and intravenous fluids should be employed concurrently with the picrotoxin therapy. An intravenous barbiturate should always be on hand to combat any incidental overdosage with picrotoxin.

#### ABBOTT LABORATORIES

**Solution Picrotoxin 0.3% :** 20 cc. vials. Each cubic centimeter contains picrotoxin 3 mg. and benzyl alcohol 0.9 per cent, in isotonic solution chloride solution.



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## CHAPTER XI

# Contraceptives

When protection from pregnancy is considered advisable, contraceptives are used to prevent passage of active spermatozoa from the vagina into the uterus. This is accomplished mechanically by occlusive devices, such as diaphragms, which lengthen the route which the spermatozoa must travel to reach the os, thereby assuring extensive exposure to a spermicidal jelly or cream. Contraceptive jellies and creams act as chemical agents immobilizing the spermatozoa with which they come into contact. Because of their consistency they also have an obstructive function. Certain accessory devices are used with these, such as inserters and extractors for the diaphragms, and syringe applicators for the jellies and creams. In control of conception acceptability probably plays a greater role in the use and therefore the effectiveness of a prescription than in most fields of medicine. The esthetic block or reluctance toward various methods differs with different users, and variation of method by a single user is often found to lead to greater acceptability and consequently a higher degree of protection.

When contraceptive preparations are prescribed, the physician should warn that there must be strict adherence to his directions. To do otherwise invites decrease in expected effectiveness. No one method can be guaranteed as being 100 per cent effective, although a high degree of protection can be expected if the patient has been properly examined and informed by the physician. The status of conception control has been reviewed in a report of the Council which appeared in *The Journal*, Dec. 18, 1943, p. 1043.

### Criteria for Acceptability of Contraceptive Jellies, Creams and Other Chemical Agents and of Syringe Applicators and Nozzles

For guidance in reviewing contraceptive products, the Advisory Committee on Contraceptives of the Council on Pharmacy and Chemistry has proposed the following criteria. These have been adopted by the Council but it should be emphasized that they may be changed from time to time. As the experience of the committee and the Council grows, improvements may appear desirable.

1. The use of the word "contraceptive" need not be limited to materials which will prevent conception on every occasion of use.
2. Evidence shall be furnished that use of the material decreases the incidence of pregnancy. This evidence may be secured

in connection with occlusive devices unless the manufacturer's advertising is directed chiefly toward the use of the jelly or cream without such devices. It is desirable that each case reported should be observed for at least twelve months, and that the minimum of 75 patient-years of experience should be reported. If cases are excluded from the series on the basis of their being irregular users, the number excluded and the nature of the evidence justifying their exclusion should be stated.

3. Evidence shall be submitted that 100 or more couples have used the material on six or more occasions without subjective injury.

4. Evidence shall be submitted that 12 or more women have received vaginal applications of the recommended dosage on twenty-one successive days without subjective irritation or injury and without evidence of physical damage shown on speculum examination by a physician with special experience in this field. Inspection of the vagina once a week should be done as a protection to the patient in case the jelly proves to be irritating.

5. The quantitative formula from which the contraceptive mixture is prepared shall seem to the Advisory Committee to be safe and, presumably, effective.

6. The consistency shall be satisfactory to the committee. It shall not show separation into more liquid and more solid portions visible to the naked eye.

7. Evidence shall be submitted that the consistency is not substantially changed after storage for twelve months at 27 C.

8. The consistency shall be reasonably uniform from batch to batch.

9. The spermicidal time of the contraceptive material as measured by the method of Brown and Gamble (*Human Fertil.* 5:97 [Aug.] 1940) with proportions of material, isotonic solution of sodium chloride and semen of 1:4:5 shall be thirty minutes or less as measured by the average of four or more tests.

10. The use of jellies or creams suggested by the manufacturer need not be limited to use in conjunction with an occlusive device.

11. If a syringe applicator or nozzle is furnished for use in connection with the jelly or cream, it shall be sufficiently translucent to permit the detection of air which might lead to inadequate dosage.

12. If a perfume is used, a quantitative statement of ingredients is desired.

#### Criteria for Acceptability of Contraceptive Diaphragm or Cap

Criteria for the acceptability of contraceptive diaphragms and accessory devices, such as inserters and extractors, have been adopted by the Council on Physical Medicine. The following physical devices accepted by the Council on Physical Medicine are intended to accompany or are available by the same dis-

tributors of accepted chemical contraceptives: Ortho Diaphragms, Ramses Diaphragms, Ramses Diaphragm Introducer, and Ramses Fitting Rings.

### Contraceptive Preparations

#### CONTRACEPTIVE JELLIES AND CREAMS

*Actions, Uses and Dosage.*—Jellies and creams for contraceptive use are usually introduced into the vagina by means of the occlusive diaphragm or cervical cap with which they are used. This should be done not more than 12 hours before sexual intercourse. A portion of the dose of jelly or cream is placed on the rim of the occlusive device, the balance on the upper side, the side which will be in contact with the cervix. A few physicians recommend the subsequent introduction of additional jelly or cream close to the occlusive device by means of a syringe applicator.

Jellies and creams may also be used without an occlusive device, but this may result in a lower degree of protection. Some users find this technic definitely more acceptable, sufficiently so to outweigh the difference in fertility rate. When used without an occlusive device the jelly or cream is introduced into the vagina within an hour before intercourse by a syringe applicator. The recommended dose varies but is usually approximately 5 cc. To allow adequate time for the chemical to immobilize the spermatozoa, the occlusive device should not be removed nor should a douche be taken within six hours of ejaculation.

As most of the contraceptive diaphragms are made of rubber, which will deteriorate if exposed to greases, the jellies and creams used should not contain greasy substances, such as lanolin and petrolatum.

Applicators are designed for ready filling from the container of contraceptive jelly or cream and for delivery under moderate pressure of the recommended dose (usually 5 cc.) into the upper vagina. They should be transparent, to permit detection of air which might lead to inadequate dosage, and, if made of glass, should be sufficiently thick walled to make breaking while in the vagina extremely improbable. The end should be blunt, and sufficiently large to prevent entry into the urethra.

#### CONTRA CREME AND DIAPHRAGM CO.

**Contra Creme:** 63.5 Gm. collapsible tubes. A stearic acid cream having a pH of 7.3, packaged from the formula:

	Per Cent
Phenylmercuric acetate .....	0.06
Stearic acid .....	12.0
Triethanolamine .....	0.06
Glycol monostearate .....	3.5
Glycerin .....	2.5
Distilled water to make .....	100.00

Packaged with a Contra Applicator or in refill packages containing a tube of cream only.

U. S. trademark 355,838.

**Contra Applicator:** A transparent plastic syringe threaded at the blunt intravaginal end, to screw onto the tubes of Contra Creme, to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose.

DUREX PRODUCTS, INC.

**Lactikol Creme:** 56.5 Gm., 85 Gm. and 116 Gm. collapsible tubes. A water dispersible nonfatty stearic acid and glyceryl monostearate cream, having a  $p_H$  of 4.9, prepared from the formula:

	Per Cent
Lactic acid .....	0.50
Stearic acid .....	15.00
Sodium lauryl sulfate .....	0.60
Glyceryl monoricinoleate .....	1.50
Glyceryl monostearate .....	7.50
Glycerin .....	8.00
Perfume .....	0.07
Water sufficient to make.....	100.00

Packaged with a Lactikol Applicator or in refill packages containing a tube of cream only.

**Lactikol Jelly:** 62.5 Gm., 93.5 Gm. and 128 Gm. collapsible tubes. A water soluble jelly formed from tragacanth, karaya and acacia, having a  $p_H$  of 4.15, prepared from the formula:

	Per Cent
Lactic acid .....	1.50
Oxyquinolin sulfate .....	0.05
Butyl <i>p</i> -hydroxy benzoate .....	0.02
Sodium lauryl sulfate .....	0.20
Glyceryl monoricinoleate .....	1.00
Glycerin .....	16.00
Tragacanth .....	2.70
Karaya .....	1.00
Acacia .....	1.00
Perfume .....	0.04
Water sufficient to make.....	100.00

Packaged with a Lactikol Applicator or in refill packages containing a tube of jelly only.

**Lactikol Plunger Applicator:** A transparent plastic tube threaded at the blunt intravaginal end to screw onto the tubes of Lactikol Creme and Jelly to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose.

**Lactikol Metri-Dose Applicator:** A transparent glass tube graduated to permit delivery of from 5 to 8 cc., slightly constricted at the intravaginal end to fit the tubes of Lactikol Creme or Jelly, and fitted at the distal end with a rubber compression bulb with central wire spring device to permit adjustment of the volume of jelly or cream to be delivered.

EATON LABORATORIES, INC.

**Lorophyn Jelly:** 92 Gm. collapsible tubes. A water soluble jelly formed from tragacanth and purified Irish moss, having a  $p_H$  of 7.5, prepared from the formula:

	Per Cent
Phenylmercuric acetate .....	0.05
Sodium borate, U. S. P. ....	3.0
Methyl-p-hydroxybenzoate .....	0.05
Polyethylene glycol of monoisooctylphenyl ether.....	0.3
Gum tragacanth .....	1.8
Purified Irish moss .....	1.2
Glycerin .....	8.0
Water sufficient to make .....	100.00

Packages containing a tube of jelly only. Lorophyn Jelly Applicators are supplied in separate cartons.

U. S. patent 2,436,184.

**Lorophyn Jelly Applicator:** A transparent plastic syringe threaded at the blunt, intravaginal end, to screw onto the tubes of jelly, to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose.

HOLLAND-RANTOS Co., INC.

**Koromex Cream:** 78 Gm. and 113 Gm. collapsible tubes. A water soluble stearic acid emulsion having a pH of 4.2 to 4.4 prepared from the formula:

	Per Cent
Phenylmercuric acetate .....	0.02
Boric acid .....	2.0
Oxyquinolin benzoate .....	0.02
Stearic acid .....	20.0
Butyl-p-hydroxybenzoate .....	0.02
Sorbitan monooleate .....	5.0
Polyoxyalkalene sorbitan monostearate .....	3.0
Cetyl alcohol .....	1.0
Glycerin .....	5.0
Perfume .....	0.015
Water sufficient to make .....	100.00

Packaged with a vaginal applicator or in refill packages containing a tube of cream only.

U. S. trademark 213,756.

**Koromex Jelly:** 85 Gm. and 128 Gm. collapsible tubes. A water soluble jelly formed from tragacanth and gum acacia having a pH of 4.6, prepared from the formula:

	Per Cent
Phenylmercuric acetate .....	0.02
Boric acid .....	2.0
Oxyquinoline benzoate .....	0.02
Butyl-p-hydroxybenzoate .....	0.02
Glycerin .....	10.0
Gum acacia .....	0.6
Tragacanth .....	2.5
Perfume .....	0.015
Water sufficient to make .....	100.00

Packaged with a Koromex Vaginal Applicator or in refill packages containing a tube of jelly only.

U. S. Trademark 213,756.

**Koromex Vaginal Applicator:** A transparent plastic tube threaded at the blunt, intravaginal end, to screw onto tubes of Koromex Jelly to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose.

## THE SPECIAL FORMULA CORPORATION

**Lygel Vaginal Cream:** 85 Gm. collapsible tubes. A white stearic acid cream having a pH of 3.4, prepared from the formula:

	Per Cent
Lactic acid .....	0.35
Stearic acid .....	18.00
p-chloro-symm.m.—Xylenol .....	0.10
p-tert. amylphenol .....	0.10
Cetyl alcohol .....	4.00
Nacconol .....	2.00
Sorbitol .....	6.00
Perfume .....	0.10
Water sufficient to make .....	100.00

Packaged with a Lygel Vaginal Applicator or in refill packages containing a tube of cream only.

**Lygel Vaginal Jelly:** 92 Gm. collapsible tubes. A water soluble jelly having a pH of 3.4 prepared from the formula:

	Per Cent
Lactic acid .....	0.25
Benzalkonium chloride .....	0.10
p-tert. amylphenol .....	0.05
Glycerol .....	15.00
Gum tragacanth and pectin .....	3.50
Perfume oil .....	0.10
Water, sufficient to make .....	100.00

Packaged with a Lygel Vaginal Applicator or in refill packages containing a tube of jelly only.

U. S. patent 1,953,413 (April 3, 1934).

U. S. trademarks 343,141 and 348,042.

**Lygel Vaginal Applicator:** A transparent plastic syringe threaded to screw onto the tubes of Lygel Vaginal Jelly, to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose.

U.S. patents 1,918,706; 2,077,176; 2,161,178.

## ORTHO PHARMACEUTICAL CORP.

**Ortho-Creme:** 75 Gm. collapsible tubes. A nonfatty stearic acid cream having a pH of 6, prepared from the formula:

	Per Cent
Stearic acid .....	24.00
Boric acid .....	2.00
Ricinoleic acid .....	0.75
Cetyl alcohol .....	0.50
Sodium lauryl sulfate .....	0.28
Triethanolamine .....	0.25
Glycerin .....	8.00
Perfume .....	0.05
Water sufficient to make .....	100.00

Packaged with an Ortho Vaginal Applicator or in refill packages containing a tube of cream only.

U. S. patent 2,330,846 (Oct. 5, 1943; expires 1960). U. S. trademark 390,141.

**Ortho-Gynol Vaginal Jelly:** 90 Gm. collapsible tubes. A water soluble jelly formed from tragacanth and acacia, having a pH of 4.5 prepared from the formula:

	Per Cent
Boric acid .....	3.00
Ricinoleic acid .....	0.75
Oxyquinoline sulfate .....	0.025
Propyl-p-hydroxybenzoate .....	0.05
Glycerin .....	10.00
Acacia .....	2.00
Tragacanth .....	3.00
Perfume .....	0.025
Water sufficient to make .....	100.00

The consistency is indicated by a 50-55 mm. dart penetration at 40 C. when tested with the Braun dart penetrometer.

Packaged with an Ortho Vaginal Applicator or in refill packages containing a tube of jelly only.

U. S. trademark 298,222.

**Ortho Vaginal Applicator:** A transparent plastic syringe threaded at the blunt intravaginal end, to screw onto the tubes of Ortho-Gynol Vaginal Jelly or Ortho-Creme, to permit filling by compression of the tube. The full capacity is 5 cc., the recommended dose.

U. S. trademark 394,998.

**JULIUS SCHMID, INC.**

**Ramses Vaginal Jelly:** 92 Gm. collapsible tubes. A water soluble jelly formed from carborymethylcellulose and glycerin having a pH of 4, prepared from the formula:

	Per Cent
Dodecaethylene glycol monolaurate .....	5.00
Boric acid .....	1.00
Alcohol .....	5.00
Carboxymethylcellulose .....	2.50
Glycerin .....	9.00
Butyl parahydroxybenzoate .....	0.02
Perfume .....	0.01
Water sufficient to make .....	100.00

Packaged with a Ramses Vaginal Applicator or in refill packages containing a tube of jelly only.

U. S. trademark 306,696.

**Ramses Vaginal Applicator:** A transparent plastic tube threaded at the blunt intravaginal end to screw onto the tubes of Ramses Jelly to permit filling by compression. A plastic cylinder fitted inside the tube permits the operator to expel the jelly. The full capacity is 5 cc., the recommended dose.

U. S. patents 1,918,706 and 2,077,176.

**WHITTAKER LABORATORIES, INC.**

**Cooper Creme:** 75 Gm. collapsible tubes. A white, non-greasy, water miscible stearate cream having a pH of 7.3 prepared from the formula:

	Per Cent
Stearic acid .....	23.04
Trioxymethylene, U. S. P. ....	0.04
Diocetyl sodium sulfo succinate .....	0.50
Sodium oleate .....	0.67
Trihydroxyethylamine .....	7.91
Hydrous aluminum silicate .....	2.34
Perfume (compounded oil of lavender) .....	
Water sufficient to make .....	100.00

Packaged with a Cooper Creme Dosimeter or in refill packages containing a tube of cream only.

**Cooper Creme Dosimeter:** A transparent plastic tube, threaded at the blunt intravaginal end to screw onto the tubes of Cooper Creme to permit filling by compression of the tube. The full capacity of the dosimeter is 10 cc.

## CONTRACEPTIVE CAPSULES AND SUPPOSITORIES.

*Actions and Uses.*—Capsules and suppositories provide a convenient method for introducing obstructive and spermicidal material into the vagina with the advantage of freedom from the need of apparatus. The solid material introduced must be converted to a jelly or liquid form in order to cover the requisite area; hence prompt liquefaction is important. For some suppositories this results from a melting point below the temperature of the body. For others the active material is enclosed in a gelatinous shell which melts or opens when exposed to body temperature and moisture. The time required should be under ten minutes, and the users should be instructed to allow more time than this, at least fifteen minutes, to elapse before intercourse. A douche should not be taken less than six hours after ejaculation.

To insure further protection, physicians should advise the concurrent use of an occlusive device such as a diaphragm, and should stress the fact that suppositories or capsules used alone are less effective.

### EATON LABORATORIES

**Lorophyn Vaginal Suppositories:** Suppositories consist of low melting mass prepared from the formula:

	Per Cent
Phenylmercuric acetate .....	0.05
Glyceryl mono-laurate .....	10.00
Tween 61 (Sorbitan monostearate)hydroxy polyoxyethyl ene ether .....	89.95

*Dosage.*—One suppository containing 3 Gm.

### PERNOX, INC.

**Pernox Vaginal Capsules:** A soft gelatin capsule containing a low melting mass prepared from the formula:

Ricinoleic acid .....	0.045 Gm.
Propylene glycol monostearate .....	1.830 Gm.
Propylene glycol .....	0.183 Gm.
Diocetyl sodium sulfosuccinate .....	0.045 Gm.
Cholesterin bodies .....	0.220 Gm.



Anhydrous lanolin .....	1.100 Gm.
Liquid petrolatum .....	0.770 Gm.
Yellow petrolatum .....	0.110 Gm.
Tragacanth .....	0.214 Gm.

*Dosage.*—One capsule, containing 4.5 Gm.

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## CHAPTER XII

# Diagnostic Aids

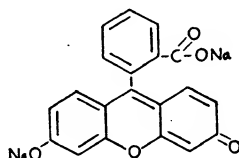
In this chapter are assembled various drugs whose use internally or externally helps to reveal the anatomical evidences of disease or whose excretion from the body furnishes a physiological test of renal or hepatic function. The list includes barium and iodine compounds used as contrast media in roentgenography, certain dyes used in testing the functional capacity of the kidneys and liver, and antigenic preparations not classed with Agents Used in Allergy or Serums and Vaccines.

Allergenic extracts used for diagnosis are included in the chapter on Agents Used in Allergy. Toxins used in immunity tests are described in the chapter on Serums and Vaccines.

### External

**FLUORESCEIN SODIUM-U. S. P.**—"When dried to constant weight at 105 C., contains not less than 98.5 per cent of  $C_{20}H_{10}O_5Na$ ." *U. S. P.*

Fluorescein is formed by condensing resorcinol with phthalic anhydride. Fluorescein sodium may be represented by the following structural formula:



For description and standards see the U. S. Pharmacopeia under Fluorescein Sodium.

Fluorescein is closely related to phenolphthalein from which it differs in structure by the presence of an oxygen bridge linking the phenol nuclei in their ortho positions. In common with the phthaleins, it forms salts with alkali whereby a rearrangement takes place and the quinolyl group is formed. Fluorescein is brominated easily to form the beautiful dye eosin, the tetrabromo derivative.

**Actions and Uses.**—The soluble sodium salt of fluorescein (fluorescein 2 Gm., sodium bicarbonate 3 Gm., water to make 100 cc.) has been used for the diagnosis of corneal lesions and the detection of minute foreign bodies embedded in the cornea.

While a weak solution of fluorescein will not stain the normal cornea, ulcers or parts deprived of epithelium will become green and remain so for a time; foreign bodies will appear surrounded by a green ring; loss of substance in the conjunctiva is indicated by a yellow hue. Fluorescein also reveals defects or disease of the endothelium of the cornea, producing a deep coloration of the diseased area.

MERCK & Co., INC.

**Fluorescein (Powder).**

**TRICHINELLA EXTRACT.**—Trichinella extract is diluted saline extraction of clean Trichinella larvae prepared by artificial digestion of muscles of heavily infested experimental animals. The extract is adjusted to neutrality and sterilized by filtration.

*Actions and Uses.*—Trichinella extract is used for making the intradermal diagnostic skin test in the diagnosis of trichinosis. An immediate or delayed type of positive reaction may result from the intradermal injection of 0.1 cc. of the diluted antigen, depending on the duration of the illness.

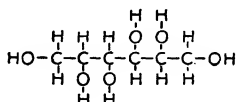
ELI LILLY AND COMPANY

**Trichinella Extract:** Two 1 cc. vials; one vial of Trichinella Extract, 1:10,000 dilution in isotonic solution of sodium chloride; and one control vial of isotonic solution of sodium chloride used as extracting fluid. Both extract and control solution contain Merthiolate, 1:20,000, as a preservative.

## Internal

### *Agents Used for Kidney Function Tests*

**MANNITOL.**—1,2,3,4,5,6-hexahydroxyhexane.—A hexahydroxy alcohol related to mannose. The structural formula of mannitol may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Mannitol is a hexahydric alcohol which is filtered at the glomeruli but is neither reabsorbed nor excreted by the tubules. Mannitol may be used to measure glomerular filtration. The normal values for the glomerular filtration rate are  $131 \pm 21.5$  cc. per minute for men and  $117 \pm 15.6$  per minute for women. These values are corrected to a standard surface area of 1.73 square meters. In the presence of renal disease

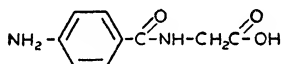
in which the glomeruli are damaged, values lower than normal are found. The validity of results of clearances with mannitol is questioned by some observers.

**Dosage.**—Mannitol is administered as a sterile 25 per cent solution by venoclysis. The concentration of mannitol is determined in milligrams per cubic centimeter of blood plasma. The urine formed during a definite period is collected, and the mannitol excreted is calculated in milligrams per minute. The glomerular filtration rate in cubic centimeters per minute is calculated from these two values and is equivalent to the number of cubic centimeters that must have been filtered at the glomerulus to supply the amount of mannitol excreted in the urine per minute.

SHARP & DOHME, INC.

**Solution Mannitol:** 50 cc. ampuls. Each ampul contains 12.5 Gm. mannitol.

**PARA-AMINOHIPPURIC ACID.**—4-aminobenzoylglycine.—The N-acetic acid amide of para-aminobenzoic acid.—The structural formula of para-aminohippuric acid may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Sodium para-aminohippurate is excreted by the tubular epithelium of the kidneys in addition to being filtered by the glomerulus. It may be used to measure the effective renal plasma flow and to determine the functional capacity of the tubular excretory mechanism. To measure renal plasma flow, low plasma concentrations (1.0 to 2.0 mg. per 100 cc.) are necessary. At these concentrations 88 per cent of this compound is removed from the renal blood stream in a single circulation. The normal effective renal plasma flow is  $697 \pm 135.9$  per minute for men and  $594 \pm 102.4$  cc. per minute for women. This test cannot be applied to patients receiving sulfonamide compounds, because these develop color with the reagents used in the test.

To determine the functional capacity of the tubular excretory mechanism high plasma concentrations (above 60 mg. per 100 cc.) of sodium para-aminohippurate must be used. The normal mean value of the "tubular excretory mass" is  $77.5 \pm 12.9$  mg. per minute.

**Method of Application.**—To Determine Effective Renal Plasma Flow: Sterile solution of sodium para-aminohippurate is injected intravenously in a volume sufficient to produce approximately 2 mg. of para-aminohippurate per 100 cc. of blood plasma. At this plasma level all the para-aminohippurate in the

blood that passes through the kidney is removed and appears in the urine. The urine formed during a definite but relatively short period is collected, and the average amount of para-aminohippurate eliminated is calculated in milligrams per minute. This value divided by the para-aminohippurate content of the plasma in milligrams per cubic centimeter is equivalent to the number of cubic centimeters of plasma per minute that must have passed through the kidneys (effective renal plasma flow).

**To Determine Tubular Excretory Mass:** Sterile solution of sodium para-aminohippurate is injected intravenously in a volume sufficient to "saturate" the capacity of the tubular cells to excrete para-aminohippurate (above 60 mg. per 100 cc. of plasma), and the para-aminohippurate content of the plasma is determined in milligrams per cubic centimeter. The amount excreted in the urine is determined in milligrams per minute, this value including both glomerular filtration and tubular excretion. The glomerular filtration rate, using mannitol, a compound that is filtered only through the glomerulus, is determined in cubic centimeters per minute (see description of Sterile Solution of Mannitol). From the glomerular filtration rate and the para-aminohippurate content per cubic centimeter of plasma is calculated the amount of para-aminohippurate that was filtered through the glomeruli in one minute ( $\text{cc./min.} \times \text{mg./cc.}$ ). Then the total number of milligrams excreted in the urine per minute minus that amount filtered through the glomeruli per minute equals the amount of para-aminohippurate in milligrams per minute excreted by the tubules (tubular excretory mass).

SHARP & DOHME, INC.

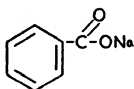
**Solution of Sodium Para-Aminohippurate:** 50 cc. ampuls. Each 50 cc. contains 10 Gm. of sodium para-aminohippurate, buffered to pH 7.0 with citric acid.

**Para-Aminohippuric Acid (Reagent):** 2 Gm. vials. For use in the preparation of standard solutions.

**PHENOSULFONPHTHALEIN**—See section on Phenolphthalein dyes.

### *Benzoic Acid Derivatives*

**SODIUM BENZOATE**—U. S. P.—"When dried at 100 C. for 4 hours, contains not less than 99 per cent of  $\text{C}_6\text{H}_5\text{COONa}$ ." U. S. P. The structural formula may be represented as follows:



For standards see the U. S. Pharmacopeia under Sodium Benzoate.

**Actions and Uses.**—The intravenous use of sodium benzoate as a liver function test was suggested by Quick and his co-workers in 1938 (Quick, A. J.; Ottenstein, H. N., and Weltcheck, Herbert: *Proc. Soc. Exper. Biol. & Med.* 38:77 [Feb.] 1938) to overcome the disadvantages associated with its oral administration. In the presence of normal liver function in man, benzoic acid is excreted as hippuric acid. The rate at which this material is excreted determines the functional ability of the liver and often demonstrates the presence of liver damage before clinical signs are evident.

The test is contraindicated in the presence of renal disease, because here the hippuric acid is but partially eliminated.

**Dosage.**—The bladder is emptied before administration of the drug. Inject *slowly*, intravenously, 20 cc. of sodium benzoate solution containing 1.77 Gm. of the salt (equivalent to 1.5 Gm. of benzoic acid), using not less than five minutes for the injection. Exactly one hour after the injection a complete urine specimen is collected and the amount of hippuric acid determined by the method developed by Quick (Quick, A. J.: *Am. J. Digest. Dis.* 6:716 [Dec.] 1939).

An adult with a normal liver will excrete at least 1 Gm. of hippuric acid (equivalent to 0.68 Gm. of benzoic acid) within one hour after receiving sodium benzoate intravenously.

GEORGE A. BREON & COMPANY, INC.

**Solution Sodium Benzoate:** 1.77 Gm. (equivalent to 1.5 Gm. benzoic acid) in 20 cc. ampuls.

### *Barium Sulfate*

**BARIUM SULFATE-U. S. P.**—Skiabaryt-Merck.— $\text{BaSO}_4$ .—For description and standards see the U. S. Pharmacopeia under Barium Sulfate.

**Actions, Uses and Dosage.**—Barium sulfate for roentgen examination, being freed from soluble barium and other salts, passes unchanged through the digestive tract and because of this is used in taking roentgenograms of the stomach and of the intestines.

**For Roentgen Examination of the Stomach.**—A barium sulfate suspension usually is made to contain 300 Gm. of the sulfate in 400 cc. of water, but the amount of water may vary according to the thickness of mixture desired.

**For Roentgen Examination of the Colon.**—A barium sulfate suspension is made to contain 750 Gm. of the sulfate in 1,500 cc. of water.

The patient should be prepared by the administration of 1 ounce of castor oil the night before the examination and of a plain water or saline enema two hours before the procedure is performed.

The suspension warmed to body temperature is injected into the rectum by enema tube from a height of 90 to 180 cm.

*Caution.*—When Barium Sulfate is prescribed, the title should always be written out in full to avoid confusion with the poisonous barium sulfide or sulfite. U. S. P.

MALLINCKRODT CHEMICAL WORKS

Barium Sulfate for X-Ray Diagnosis: bulk.

MERCK & Co., INC.

Barium Sulfate for X-Ray Diagnosis: bulk.

**Skiabaryt for Oral Administration:** A mixture of barium sulfate, 80 to 85 per cent, sugar, tragacanth, vanillin, cinnamon and cacao.

**Skiabaryt for Rectal Administration:** A mixture of barium sulfate U. S. P., 95 per cent, sugar and tragacanth.

U. S. trademark 165,022.

### *Iodized Oils*

Iodized oils are injected as contrast mediums in roentgen diagnosis, especially of tumors of the spinal cord; in the localization of bronchial and pulmonary lesions; and in gynecology. Various vegetable oils may be used; animal oils cause local irritation. According to the method of iodination, the oil may contain iodine alone, or iodine and chlorine ("chloriodized oils"). These do not differ essentially.

Iodized oils are quite viscid. For injections into cavities they may be rendered less viscid by the addition of ethyl oleate; they may be rendered water-miscible by emulsification.

*Caution.*—"It should be emphasized that the injection of iodized oils is essentially a surgical procedure, introducing a foreign and possibly irritant body, and involving more or less risk, which should be weighed against the presumptive advantages, in comparison with the relative advantages and disadvantages of other measures. The following cautions should be especially borne in mind:

"1. Oils that have aged and darkened beyond their original color should never be used.

"2. Subarachnoid injections should be avoided, at least until all other means of diagnosis have been exhausted.

"3. Intratracheal and intrapleural injections should be avoided in tuberculosis of the respiratory organs and also when restriction of respiratory area would be contraindicated.

"4. The injection pressure should be carefully controlled, so as not to lacerate the tissues.

"5. Intra-uterine injections should be made only under fluoroscopic observations.

"6. Iodized oil should not be used for renal pyelography, except in the form of emulsion; and the injection should be stopped if pain is felt.

"7. Intravascular injections with iodized oil appear too dangerous; the use of emulsions for this purpose requires further

study." (Dangers of the Injection of Iodized Oils, Report of the Council on Pharmacy and Chemistry. *The Journal*, A. M. A. 99: 1946, Dec. 3, 1932. The full report may be consulted for further discussion of the history, scope and limitations of iodized oils.)

8. When the so-called per-nasal method of injecting the oil into the larynx is employed, it should be remembered that in the injection of the local anesthetic required for this procedure, the risk of intoxication from the anesthetic is greatly enhanced as the absorptive surface is increased.

**IODIZED OIL-U. S. P.**—Lipiodol, 40% Iodine-Fougera. —Lipiodol 40% Iodine Radiologique Descendant-Fougera. —"An iodine addition product of vegetable oils, containing not less than 38 per cent and not more than 42 per cent of organically combined iodine (I)." *U. S. P.*

For description and standards see the U. S. Pharmacopeia under Iodized Oil.

*Actions and Uses.*—Iodized oil is used as a substitute for inorganic iodides; and as a contrast medium in roentgenography. See general article, Iodized Oils. In subarachnoid injection for roentgen examination, iodized oil is used for the recognition of intradural tumors.

*Dosage.*—From 1 cc. to 5 cc. or more according to the uses to which it is to be put.

E. FOUGERA & COMPANY, INC.

**Solution Lipiodol in Oil (40% Iodine):** 1 cc., 2 cc., 3 cc. and 5 cc. ampuls and 20 cc. neoprene-capped flask. An iodine addition product of poppy seed oil.

**Solution Lipiodol in Oil (40% Iodine Radiologique Descendant):** 5 cc. flasks.

U. S. trademark 196,499.

**IODOBASSID.**—Lipoiodine-Ciba.—Ethyl Diiodobrassidate.— $\text{CH}_3(\text{CH}_2)_7\text{CHI}.\text{CHI}(\text{CH}_2)_{11}\text{COOH}$ .—Iodobrassid contains 41 per cent of iodine. Its structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Iodobrassid is used as a substitute for the inorganic iodides and as a contrast medium for roentgenologic work. See general article, Iodized Oils.

For diagnostic work, from 5 to 20 cc. of Iodobrassid, as determined by the extent of the field to be investigated.



CIBA PHARMACEUTICAL PRODUCTS, INC.

**Solution Lipoiodine in Oil (Diagnostic):** 10 cc. bottle. A 60 per cent solution of lipoiodine in sesame oil.

**Tablets Lipoiodine:** 0.3 Gm.

U. S. patent 1,024,171 (April 23, 1912; expired).

U. S. trademark 81,554.

**LIPIODOL RADIOLOGIQUE ASCENDANT-Fougera.**—Iodized Poppy-Seed Oil 10 per cent.—An iodine addition product of poppy-seed oil containing 9.8 to 11.2 per cent of iodine (0.11 Gm. of iodine per cc.) in organic combination.

For tests and standards, see Section B.

**Actions and Uses.**—Lipiodol Radiologique Ascendant is used for recognition of intradural tumors when it is desired to employ a contrast medium of lesser density than that of the spinal fluid.

**Dosage.**—From 1 to 2 cc., previously brought, with the syringe, to a temperature of 40 C.

E. FOUGERA & COMPANY, INC.

**Solution Lipiodol in Oil (Radiologique Ascendant):** 5 cc. flasks.

U. S. trademark 196,499.

### ***Water-Soluble Organic Iodine Compounds for Roentgenography***

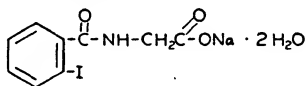
Satisfactory roentgenograms of the urinary tract may be secured by the intravenous injection of soluble iodine compounds of low toxicity, which are rapidly excreted by the urine. Several organic compounds are now available for this use. Sodium iodide, in the necessary dose, is too toxic for intravenous injection. The organic compounds may also be used for ureteral retrograde pyelography.

For intravenous urography, it is now generally accepted that no fluids should be given to the patient for several hours (usually from midnight) prior to examination. Restriction of fluids permits greater concentration of the drug. The gastro-intestinal tract should be cleared of gas and retained materials by enemas and laxatives, preferably of castor oil. The excretory urogram should be made by those who are experienced with this method and during the entire procedure the patient should be watched for untoward reactions. Ocular, oral and intradermal tests that have been proposed to detect sensitivity to intravenously administered iodine compounds are not reliable in predicting possible reactions that are apparently more often due to a direct vascular effect. The medium should be given slowly, pausing after 1 or 2 cc. are injected to see if a reaction may occur. Care should be exercised to ensure that all the solution is injected into the

vein. Side effects which may be encountered include flushing of the face and neck, urticaria, fall in blood pressure, nausea, vomiting, lacrimation, salivation, edema of the glottis, bouts of coughing, "tight feeling" or choking sensation, and cyanosis. Usually these symptoms disappear over varying periods of time but fatalities have been encountered. Any history of allergy should be elicited before injection. If there is reason to suspect that a reaction may occur a small initial dose may be given first. In any event, epinephrine hydrochloride 1:1,000 should be available when the injection is made. The intravenous use of the drug is contraindicated in patients with severe liver disorders, nephritis and severe uremia, and it should be used with caution in cases of active tuberculosis and of hyperthyroidism. Excretory urography should not be used routinely in all patients. Further, this method may have to be checked with retrograde pyelography, and either or both methods closely correlated with the clinical findings. Injection of the medium into the kidney pelvis is most accurately gauged by using a manometer, but lacking this instrument gravity or a syringe may be employed for retrograde pyelography if care is exercised. Because of reflex splanchnic stimulation, anuria, especially after bilateral examination, has been reported. Excretory urography or retrograde pyelography should not be repeated too soon.

The compounds may be used for venograms in the study of varicose veins.

**HIPPURAN-Mallinckrodt.**—Sodium *ortho*-iodohippurate. Hippuran contains 34.95 per cent of iodine, or 38.8 per cent when calculated to the dried substance. Its structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Hippuran is proposed for use as a radiopaque agent for intravenous, oral or retrograde urography. When used by the intravenous route, irritation at the site of injection is stated not to occur and systemic reactions appear to be unusual; a sensation of generalized warmth is the most common side-effect; nausea occurs occasionally and vomiting rarely. Fasting and dehydration of patients preliminary to administration of the drug are usually employed. Pressure over the bladder region is employed by some clinicians; this is released immediately before the first exposure and is replaced until the next. Ordinarily the first film is exposed about ten minutes after injection and two subsequent pictures are taken at fifteen or twenty minute intervals. In case excretion is delayed, later exposure may be necessary.

Results with oral administration of the drug are less satisfactory but a sufficiently high percentage of successful pictures

appear to be obtained to make this method worthy of trial in occasional cases in which intravenous or retrograde urography is not feasible. The somewhat objectionable taste of the compound usually does not militate against its ingestion. Toxic effects after oral administration have not been reported. Pictures are taken 60, 90, 120 and 150 minutes after oral administration. The use of moderate compression over the bladder region is recommended in the intervals between exposures. While the iodine in Hippuran is firmly bound, the compound should nevertheless be used with caution in patients with hyperthyroidism and tuberculosis. The intravenous use of the drug is contraindicated in severe liver disorders, nephritis and uremia. In suspected cases preliminary hepatic and renal function tests should be employed.

Satisfactory visualization has been reported with Hippuran when employed by the retrograde method for urethrograms, cystograms or pyelograms. There is said to be little or no tissue irritation with effective concentrations.

**Dosage.**—For intravenous use, 25 cc. of a solution containing 12 Gm. of Hippuran, previously warmed to body temperature, is injected into the cubital vein. Young children are given proportionately smaller doses. For oral use, 12 Gm. of Hippuran is dissolved in 75 cc. of simple syrup. For children, 10 Gm. is employed. For retrograde use, Hippuran is employed in 15 to 20 per cent solution for pyelography or 3 to 5 per cent solution for cystography. The solution may be made either by diluting the ampule solution with sterile distilled water or by dissolving the crystals in distilled water, filtering and sterilizing by heat.

#### MALLINCKRODT CHEMICAL WORKS

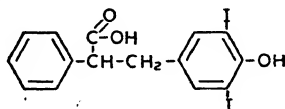
**Hippuran (Powder):** bulk.

**Hippuran (Crystals):** 12 Gm., 100 Gm. and 500 Gm. bottles.

**Solution Hippuran:** 12 Gm. in 25 cc. ampuls.

U. S. patent 2,135,474 (Nov. 1, 1938; expires 1955). U. S. trademark 314,577.

**IDOALPHONIC ACID.**—Priodax-Schering.—3-(4-Hydroxy-3,5-diiodo-phenyl)-propionic acid.—Iodoalphonic acid contains 51.38 per cent of iodine. Its structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Iodoalphonic Acid is used as a medium for cholecystography. It is claimed to cause less nausea, vomit-

ing and diarrhea than tetraiodophenolphthalein. The drug is excreted primarily through the kidneys.

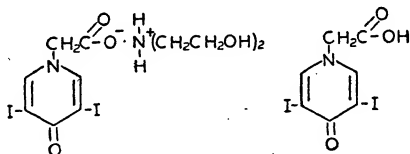
Iodoalphonic Acid is contraindicated in acute nephritis, uremia and acute disorders of the gastrointestinal tract. Side effects that may be encountered occasionally include pain on urination, nausea, vomiting, diarrhea, griping, headache, sensation of burning in the esophagus, generalized itching, dryness of the mouth, general weakness and flatulence.

**Dosage.**—The average adult dose is 3 Gm., although more may be given. The patient swallows the drug during or after a light fat-free meal in the late afternoon. Nothing is then eaten until the roentgenologic examination is completed the next morning.

SCHERING CORPORATION

Tablets Priodax: 0.5 Gm.

**IODOPYRACET COMPOUND SOLUTION.**—**Dio-drast Compound Solution-Winthrop-Stearns.**—An aqueous solution containing approximately 40.5 per cent of the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid and approximately 9.5 per cent of 3,5-di-iodo-4-pyridone-N-acetic acid. Iodopyracet compound solution contains about 25 per cent (W/V) of iodine in organic combination. The structural formulas of the diethanol amine salt of 3,5-di-iodo-4-pyridone-N-acetic acid and 3,5-diiodo-4-pyridone-N-acetic acid may be represented, respectively, as follows:



Iodopyracet compound solution is prepared by neutralizing 3,5-diiodo-4-pyridone-N-acetic acid in water with appropriate quantities of diethanolamine and diethylamine. The salts formed are soluble in water and are not isolated.

For tests and standards, see Section B.

**Actions and Uses.**—Iodopyracet compound solution is employed for roentgenographic visualization of the urinary tract by intravenous injection or by direct injection into the renal pelvis through a ureteral catheter. It is designed to provide a relatively large amount of iodine in a small volume of solution particularly for injection of obese subjects or for patients who cannot or will not cooperate in the preliminary preparation for excretion urography with iodopyracet injection. Roentgenograms should be taken at 5, 15 and 45 minute intervals after injection of the drug. Delayed, incomplete or absent shadows are given the same inter-

pretation as when iodopyracet injection is employed. The same contraindications and precautions should be observed as for iodopyracet injection.

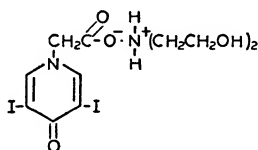
**Dosage.**—For excretion urography, iodopyracet compound solution is administered intravenously in sterile aqueous solution, the average dose for adults being 20 cc. Iodopyracet compound solution may be employed without dilution for retrograde pyelography. For economy, more dilute solutions are customarily used with satisfactory results. Eight cc. of iodopyracet compound solution when diluted with 12 cc. of sterile distilled water yields 20 cc. of 20 per cent concentration. Five cc. of iodopyracet compound solution diluted with 15 cc. of sterile distilled water (final concentration 12.5 per cent) gives wholly satisfactory pyelograms; this dilution is generally employed with excellent results in thin individuals. The volume of fluid generally required for retrograde examination in adults is 20 cc.

WINTHROP-STEARNs, INC.

Compound Solution Diodrast: 20 cc. ampuls.

U. S. patent 1,993,039 (March 5, 1935; expires 1952). U. S. trademark 312,451.

**IODOPYRACET CONCENTRATED SOLUTION.**—**Diodrast Concentrated Solution-Winthrop-Stearns.**—An aqueous solution containing 70 per cent of the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid, the structural formula of which may be represented as shown below. Iodopyracet concentrated solution contains about 44 per cent (W/V) of iodine in organic combination.



Iodopyracet concentrated solution is prepared by neutralizing 3,5-diiodo-4-pyridone-N-acetic acid in water with an equimolecular quantity of diethanolamine. The salt formed is soluble in water and is not isolated.

For tests and standards, see Section B.

**Actions and Uses.**—Iodopyracet concentrated solution is employed for use in a special diagnostic procedure for visualization of the heart, the ascending and descending aorta and branches, the superior vena cava, the pulmonary artery and branches, the coronary arteries and other structures of the heart and mediastinum. It has also been used for cholangiography by injection of the material into the common bile duct. The technic in using this agent is relatively complicated and requires accurate timing

and teamwork between the physician, the patient and the roentgenologist. The method consists in injecting the substance into the blood and taking roentgenograms simultaneously with the concentration of the opaque material in the cardiopulmonary system. In addition a preliminary examination of the chest with the x-rays is necessary to obtain data for roentgenography. At times it is necessary to determine the circulation rate of the blood for accuracy. The contraindications include hepatic disease, nephritis and hyperthyroidism. The drug should be used cautiously in the presence of heart disease and circulatory failure, never in those patients who are critically ill or in collapse. Preliminary renal function tests and determination of the patients' sensitivity should be carried out. Those with an idiosyncrasy should not be given the drug. To lessen nausea and vomiting the stomach should be empty. Side effects include dizziness, nausea, vomiting, sense of intense warmth, sweating, pallor, hypotension, transient pain at the site of injection, headache, fever, chills, cyanosis, etc. Delayed reactions may occur. Premedication with a barbiturate is advisable; epinephrine is administered when there is a possibility of an allergic reaction or low blood pressure. This technic can be mastered by experienced workers who have the proper facilities, although it might be dangerous in the hands of persons who are inexperienced or by those who use the technic in a casual manner. In skilled hands untoward reactions are comparatively few. It is claimed by the manufacturer that this agent is sufficiently stable to permit boiling for a short time if a question of sterility should arise, although the product is marketed in sterile form.

*Dosage.*—*Iodopyracet concentrated solution should not be used for excretion urography. Because of toxic possibilities it should be used intravenously only in those cases which present difficult diagnostic problems.* The amount varies according to the diameter of the chest, the size of the certain pulmonary congestion and body weight. For cardiopulmonary visualization 40 to 45 cc. may be injected intravenously. When visualization of the pulmonary circulation is desired, 30 to 35 cc. may be sufficient. If the intravenous injection must be repeated, fifteen minutes should elapse. The duration of injection should be from one and one-half to two seconds. The material should not be injected into the tissue outside the vein as irritation will result. If crystals are present warm solution to body temperature before using.

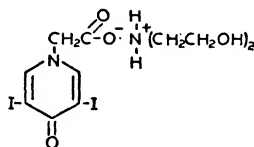
For cholangiography the amount of iodopyracet concentrated solution varies within wide limits; as little as 15 cc. and as much as 100 cc. has been required by direct injection into the common bile duct.

For description and standards see The U. S. Pharmacopeia under Iodopyracet Injection and the additional tests, as far as they apply, under Iodopyracet Compound Solution-N. N. R. (Since Iodopyracet Injection-U. S. P. is only about half the strength of Iodopyrocet Compound Solution, the quantities given in the U. S. P. standards must be multiplied by two.)

WINTHROP-STEARNs, INC.

Concentrated Solution Diodrast 70% W/V: 50 cc. ampul.

**IODOPYRACET INJECTION—U. S. P.—Diodrast—Winthrop-Stearns.**—"A solution of the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid [ $C_5H_2ONI_2CH_2COOH.NH(CH_2CH_2OH)_2$ ], containing in each 100 cc. not less than 34 Gm. and not more than 36 Gm. of the salt. The separated 3,5-diiodo-4-pyridone N-acetic acid, when dried at 100 C., contains not less than 61.5 per cent and not more than 63.5 per cent of iodine." U. S. P. The structural formula may be represented as follows:



Iodopyracet injection is prepared by neutralizing 3,5-diiodo-4-pyridone-N-acetic acid in water with an equimolecular quantity of diethanolamine. The salt formed is very soluble in water and is not isolated.

For description and standards see The U. S. Pharmacopeia under Iodopyracet Injection.

**Actions and Uses**—Iodopyracet is used as a contrast agent for intravenous urography. Local reactions about the site of injection are absent or very mild; systemic reactions occur occasionally. The latter consist chiefly of flushing of the skin with a sense of warmth; less often transient nausea, vomiting, erythematous eruptions, respiratory distress and cyanosis. These side effects usually subside within a few minutes to an hour or so without special therapy, but the skin eruptions may rarely persist for several days. In animals, iodopyracet in doses equivalent by weight to those used clinically has been found to lower the blood pressure for a period of about two hours; this slowly returns to normal and may be followed by a secondary rise; respiration is stimulated. These actions have been reported also to occur in human subjects. Fasting and dehydration of patients preliminary to injection of the drug are widely employed. The optimum time for taking roentgenograms varies between five and fifteen minutes after injection in individuals with normal kidney function (usually one exposure is made after ten minutes and a second after a further interval of ten or fifteen minutes). When renal function is impaired, this interval is proportionately longer (thirty minutes or more). A safe routine is to take roentgenograms at 5, 15 and 45 minutes after injection of the drug. Pressure over the bladder is employed by some clinicians; this is released immediately before the first exposure and is replaced until the next. The use of the drug is contraindicated in patients with severe liver disorders, nephritis and severe uremia and it

should be used with caution in cases of tuberculosis and hyperthyroidism. Preliminary renal and hepatic function tests are advisable in suspected cases. Caution should be exercised in cases in which a reduction in blood pressure would be dangerous.

**Dosage.**—Iodopyracet is usually administered intravenously in the form of an aqueous solution; each cubic centimeter contains 0.35 Gm. Twenty cc. of a solution containing 7 Gm. of iodopyracet, previously warmed to body temperature, is injected slowly, usually into the cubital veins. Children are given correspondingly smaller doses. It may be administered intramuscularly or subcutaneously in infants, children, and adults with inaccessible or obliterated arm veins, and sometimes in uncooperative, restless patients. For subcutaneous injection the adult dose (20 cc.) is diluted with 80 cc. normal saline solution; 50 cc. of this mixture are injected subcutaneously over each scapula. For intramuscular injection the dose ranges from 10 cc. to 20 cc. in children and from 20 cc. to 30 cc. in adults. One-half of the amount decided upon is injected into the right buttock and the other half into the left buttock. To prevent local discomfort a local anesthetic may be used if needed.

#### WINTHROP-STEARNs, INC.

**Solution Diodrast 35%, W/V:** 10 cc., 20 cc. and 30 cc. ampuls.

U. S. patent 1,993,039 (March 5, 1935; expires 1952). U. S. trademark 312,451.

**METHIODAL SODIUM—Skiodan-Winthrop-Stearns.**—The sodium salt of mono-iodo-methanesulfonic acid  $\text{CH}_2\text{I}\cdot\text{SO}_3\text{Na}$ .—Methiodal sodium contains 52 per cent iodine.

For tests and standards, see Section B.

**Actions and Uses.**—Methiodal sodium is proposed as a therapeutically indifferent medium for roentgenography, especially for visualization of the urinary tract either by intravenous injection or by direct injection into the renal pelvis through a ureteral catheter. It exerts a diuretic action, most marked during the first half hour after intravenous injection. Excretion studies show that within a few minutes after intravenous injection the concentration of methiodal sodium in the urine reaches a maximum of from 4 to 6 per cent (corresponding to from 2 to 3 per cent of iodine). Usually, 75 per cent is eliminated in three hours, more than 90 per cent in ten hours, and the remainder within about twenty-four hours.

The intravenous use of the drug is contraindicated in advanced renal destruction with severe uremia, severe liver disorders and exudative diathesis in children. Caution should be exercised in hyperthyroidism and tuberculosis.

**Dosage.**—For intravenous urography, methiodal sodium is administered in sterile aqueous solution (from 20 to 40 Gm. in 100 cc.), the average dosage for adults being about 2 Gm. for each 15 pounds of body weight; for retrograde pyelography an



aqueous solution of methiodal sodium (from 10 to 20 Gm. in 100 cc.) is injected through a ureteral catheter in the renal pelvis. Cystograms may be made with 3 to 5 per cent solutions. Aqueous solutions of methiodal sodium should be kept protected from light; they can be kept for a considerable time without impairment but should be resterilized before use.

For retrograde pyelography, 10 to 20 Gm. in 100 cc. methiodal sodium solution is used. In thin patients, a 10 per cent concentration often suffices. The injection is made in the customary manner through the ureteral catheter. In cases of suspected stone, some urologists prefer a 5 per cent or 6 per cent solution for thin persons, to assure satisfactory contrast. In the preparation of methiodal sodium solutions for retrograde pyelography, distilled water should be used. The solution should be sterilized by boiling or autoclaving.

On the day before the intravenous injection of methiodal sodium the patient is given a soft diet, with a cleansing enema in the evening. During the night the fluid intake is restricted as much as possible.

WINTHROP-STEARNs, INC.

**Skiodan (Powder):** 20 gram bottle.

**Solution Skiodan Sodium 20%:** 50 cc. bottles of a sterile solution of Skiodan.

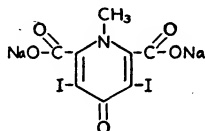
**Solution Skiodan Sodium 40%:** 50 cc. and 100 cc. bottles of a sterile solution of Skiodan.

**Tablets Skiodan:** 1 Gm. for retrograde pyelography.

U. S. patent 1,842,626 (Jan. 26, 1932; expires 1949). U. S. trademark 283,045.

**SODIUM IODOMETHAMATE.**—Neo-Iopax-Schering.—Neo-Iopax Sodium.—Disodium *N*-methyl-3, 5-diiodo-4-pyridone-2, 6-dicarboxylate.—The disodium salt of *N*-methyl-3, 5-diiodo-chelidamic acid. Sodium iodomethamate contains 51.5 per cent iodine.

The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Sodium iodomethamate is used as a contrast medium in intravenous urography and retrograde pyelography. Clinical reports indicate that systemic reactions occur uncommonly and are usually mild and fleeting. In some cases there is more or less severe pain in the arm radiating to the

shoulder; usually this disappears on completion of the injection but in a small percentage of cases it may persist for a variable period. The pain may usually be relieved by local applications of heat and the administration of an analgesic when necessary. Fluid intake should be restricted for about twelve hours prior to the examination. If only anatomic information is desired, it is usually sufficient to take a single roentgenogram from ten to twenty minutes after injection. In other cases, a series of roentgenograms are taken at intervals of five, fifteen and thirty minutes after injection. It is advisable to take a film over the urinary bladder area when making the roentgenogram thirty minutes after the injection. If the first plates show that but little of the drug has been excreted, it is presumed that the kidneys are functioning poorly, and several hours should be allowed to elapse, during which plates should be made at intervals. Impairment of renal function will allow but poor concentration of the drug; many hours are then required for its excretion. The intravenous use of the drug is contraindicated in patients with severe liver disorders, nephritis and severe uremia and it should be used with caution in cases of tuberculosis and hyperthyroidism. Caution must also be exercised in patients with any severe systemic disease. Preliminary liver and kidney function tests are advisable in suspected cases.

*Dosage.*—Twenty cc. of solution containing 15 Gm. of sodium iodomethamate previously warmed to body temperature is injected into the cubital vein. Children are given correspondingly smaller doses.

#### SCHERING CORPORATION

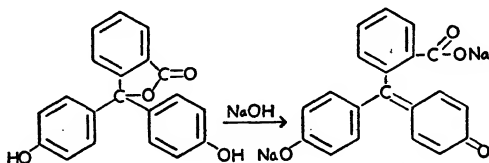
**Solution Neo-Iopax:** 10 cc. and 20 cc. ampuls. Each 1 cc. contains 0.75 Gm. of sodium iodomethamate in sterile distilled water.

**Solution Neo-Iopax:** 10 cc. and 20 cc. ampuls. Each 1 cc. contains sodium iodomethamate 0.5 Gm., dissolved in sterile distilled water.

U. S. patent 1,919,417 (July 25, 1933; expires 1950). U. S. trademark 297,925.

#### Phenolphthalein Dyes

Phenolphthalein—long used by chemists as an indicator before its therapeutic properties were discovered—is a condensation product of phthalic anhydride and phenol. In neutral and acid

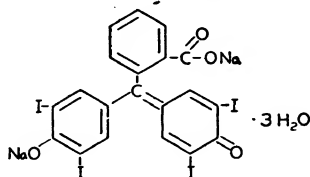


mediums it exists in a form in which there is no quinonoid group, but the presence of alkali ( $pH=8$  to  $10$ ) causes the characteristic rearrangement with typical salt formation and the presence of a quinonoid group whereby the red color is formed.

This reaction is also characteristic of other members of the series. Phenolsulfonphthalein—also used as an indicator—contains an  $SO_2$  group in place of the  $CO$  group in the phthalic anhydride nucleus. In phenoltetrachlorophthalein and phenoltetraiodophthalein the four hydrogen atoms in the benzene ring belonging to the phthalic acid nucleus have been replaced by chlorine and iodine, respectively; in tetrabromophenolphthalein, two bromine atoms are on each phenol group.

**Actions and Uses.**—All of the compounds of the phenolphthalein type are used in medicine as diagnostic agents except phenolphthalein itself. Phenolphthalein is used for its cathartic action. Phenolsulfonphthalein and phenoltetrachlorophthalein are used because they pass unchanged through the body and at the same time have the property of intense color formation when the excretions are collected and alkalinized. Bromosulfaphthalein is used in a somewhat analogous way, but instead of determining the amount excreted by the bile, the amount (not excreted) in the blood gives an index of liver function. Tetrabromophenolphthalein and tetraiodophenolphthalein—which are employed in the form of the sodium salts—are used as carriers of bromine or iodine; they appear in the gallbladder in sufficient concentration to permit the heavy halogen atoms to cast a shadow to the roentgen rays.

**IODOPHTHALEIN SODIUM-U. S. P.**—Iodeikon-Mallinckrodt.—Tetraiodophenolphthalein Sodium.—“The disodium salt of tetraiodophenolphthalein. It contains not less than 85 per cent of tetraiodophenolphthalein. The separated tetraiodophenolphthalein contains not less than 60 per cent and not more than 63 per cent of iodine(I).”—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Iodophthalein Sodium.

**Actions and Uses.**—Iodophthalein sodium is used for the roentgenologic examination of the gallbladder. Following the intravenous injection or, if decomposition is avoided, the oral administration, the substance appears in the normal gallbladder in sufficient concentration to cast a shadow to the roentgen rays. After injection, a few of the patients may have unpleasant sensa-

tions, such as dizziness, nausea, various body pains, and fall in blood pressure. The transitory fall in blood pressure may be relieved by the administration of from 0.5 to 1 cc. of epinephrine hydrochloride solution (1 in 1,000) intramuscularly. Iodophthalein sodium is useful as a diagnostic agent, but workers are cautioned as to the selection of types of cases in which it is indicated and its possible toxicity in large doses. Myocardial insufficiency and uremia are considered contraindications, and jaundice enjoins caution.

*Dosage.*—To visualize the gallbladder in a patient weighing between 52 and 73 Kg. (115 to 160 lb.), 3 Gm. of iodophthalein sodium is dissolved in 24 cc., or 3.5 Gm. of iodophthalein sodium is dissolved in 28 cc. of freshly distilled water; the solution is then sterilized by heating the container in boiling water for twenty minutes. For patients weighing over 73 Kg. pounds the maximum dose should not exceed 3.5 Gm. For patients weighing less than 52 Kg. (115 lbs.), the amount of salt is to be reduced. The solution is injected intravenously in two doses, one-half hour apart. Care must be taken not to allow extravasation, in order to avoid tissue necrosis. The injections are given at or before morning meal time but no food should be given until after the first roentgenogram is taken, usually 4 hours after the injection. A fat meal is then given and a second roentgenogram taken one hour after the meal and, if desired a third 3 hours after the meal, to determine the rapidity and characteristics of emptying. Water by mouth is allowed at all times and the evening meal is allowed as usual.

Iodophthalein sodium may be administered orally: 4 Gm. in the form of plain gelatin capsules (8 capsules of 0.5 Gm. each), or dissolved in 30 cc. of distilled water and added to 120 to 240 cc. of grape juice, to be taken during and after the evening meal, which should be of the usual amount but free of fat (the aqueous solution of the drug should not be more than 48 hours old). Keratin coated capsules may be used, the roentgenograms are then taken the following morning. Breakfast is omitted. Meticulous roentgen technic is necessary, and if the interpretation of the cholecystogram is in question a control determination should be made either by the oral or, if preferred, by the intravenous method. Iodophthalein sodium is said to be preferable for intravenous injection.

EASTMAN KODAK COMPANY

**Tetraiodophenolphthalein Sodium (Powder): Bulk.**

MALLINCKRODT CHEMICAL WORKS

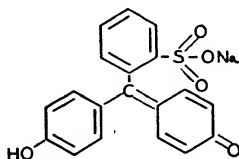
**Iodeikon (Powder): bulk.**

**Iodeikon: 3.5 Gm. ampuls iodophthalein sodium.**

MERCK & Co., INC.

**Iodophthalein Sodium (Powder): 3.5 Gm., 25 Gm., 100 Gm. and 500 Gm. bottles.**

**PHENOLSULFONPHTHALEIN-U. S. P.**—Phenol Red.  
The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Phenolsulfonphthalein and Phenolsulfonphthalein Injection.

*Actions and Uses.*—Solutions of phenolsulfonphthalein injected into the tissues are readily absorbed, and are excreted mainly in the urine. A very small amount is excreted in the feces.

Phenolsulfonphthalein is used for determining the functional activity of the kidneys. When injected intramuscularly or intravenously, it begins to be excreted in normal cases in from five to ten minutes. The average normal eliminations after intravenous administration are from 25 to 45 per cent in 15 minutes, from 50 to 65 per cent in the first hour, and a total of from 65 to 85 per cent in two hours. Following intramuscular injection 40 to 50 per cent is eliminated in the first hour and from 60 to 75 per cent at the end of two hours. The excretion of the dye is diminished in the presence of cardiac failure, particularly after intramuscular injection.

*Dosage.*—One cc. of a sterile solution, containing 6 mg. of phenolsulfonphthalein as the monosodium salt, is injected either into the lumbar muscles or into one of the antecubital veins. Great care must be taken that exactly 1 cc. is injected.

The original procedure, in which the patient was catheterized when the dye was injected and the catheter left in place until the dye was detected in the urine, is now seldom followed. From 200 to 400 cc. of water should be administered before beginning the test in order to insure free urinary secretion. If the injection is made *intramuscularly* the patient is instructed to void into a receptacle at the end of one hour and ten minutes, and into a second receptacle one hour later. If the injection is made *intravenously* the patient is instructed to void into a receptacle at the end of exactly fifteen minutes, or at the end of one hour and two hours. Slighter degrees of kidney insufficiency may be detected by a decrease in the amount of dye excreted in fifteen minutes than with longer collection periods.

The urine collected is made alkaline with a 25 per cent solution of sodium hydroxide, diluted to 1 liter, and compared with a standard containing 6 mg. of alkaline phenolsulfonphthalein per liter.

HYNSON, WESTCOTT & DUNNING, INC.

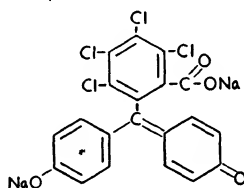
**Phenolsulfonphthalein (Powder):** bulk.

**Solution Phenolsulfonphthalein:** 1 cc. ampuls. Each 1 cc. of solution contains 6 mg. of phenolsulfonphthalein in the form of the monosodium salt.

NATIONAL ANILINE DIVISION, ALLIED CHEMICAL & DYE CORPORATION

**Phenolsulfonphthalein (Powder):** bulk.

**PHENOLTETRACHLOROPHTHALEIN.**—A dibasic dye formed by the condensation of phenol and tetrachlorophthalic acid or its anhydride. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Phenoltetrachlorophthalein has been used for the determination of the functional activity of the liver. It can be used, *in the form of the sodium salt*, intravenously; it should not be given subcutaneously or intramuscularly. It has been proposed that the excretion can be determined by any one of these methods:

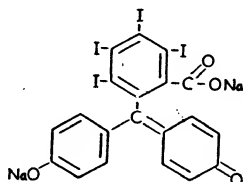
1. Its disappearance from the blood stream: S. M. Rosenthal (*J. Pharmacol. & Exper. Therap.* 19:385 [June] 1922); H. H. Rosenfield and E. F. Schneiders (*J. A. M. A.*, March 17, 1923, p. 743).

2. The excretion of the drug in the duodenum by means of a duodenal tube: Aaron, Beck and Schneider (*J. A. M. A.*, Nov. 19, 1921, p. 1631).

3. The excretion of the drug in the stool: Rowntree, Hurwitz and Bloomfield (*Bull. Johns Hopkins Hosp.* 24:327, 1913); Whipple, Peightal and Clark (*Bull. Johns Hopkins Hosp.* 24:343, 1913); Rowntree, Marshall and Chesney (*Proc. Am. A. Phys. & Surg.*, 1914; *J. A. M. A.* 63:1533 [Oct. 31] 1914).

**Dosage.**—Five milligrams in the form of disodium phenoltetrachlorophthalein per Kg. of body weight, intravenously. The solution must not be exposed unduly long, as the salt is sensitive to the action of the carbon dioxide of the atmosphere.

**PHENTETIOTHALEIN SODIUM.**—**Iso-Iodeikon-Mallinckrodt.**—Phenoltetraiodophthalein Sodium.— $\text{NaO.O}:\text{C.C}_6\text{I}_4.\text{C}:\text{C}_6\text{H}_4\text{OC}_6\text{H}_4\text{ONa}$ . Phentetiothalein sodium contains from 56 per cent to 59 per cent of iodine. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Phentetiothalein sodium is used for the roentgenologic examination of the gallbladder and simultaneous test of hepatic function. It is better suited for intravenous injection than tetiothalein sodium, because the dosage is smaller and better tolerated, and because one injection serves at the same time for cholecystography and liver function test. Following the intravenous injection the solution appears in the normal gallbladder in sufficient concentration to cast a shadow to the roentgen rays and if the liver is damaged it is retained in the blood in amounts indicative of the extent of impairment. It is claimed to cause little or no toxic reaction. Myocardial insufficiency and uremia are considered contraindications, and jaundice enjoins caution.

**Dosage.**—Intravenously for visualization of the gallbladder and simultaneous test of liver function, 40 mg. per kilogram of body weight; the dose need not exceed 2.5 Gm., regardless of weight. The dye is dissolved in about an ounce of freshly distilled water, filtered through fine filter paper, and sterilized for fifteen minutes in a boiling water bath. The solution should be freshly made not more than twenty-four hours before it is used. It is injected intravenously by gravity with about 150 cc. of Ringer's solution in not less than fifteen minutes, either in the morning between 8 and 9 or in the evening between 5 and 9. If given in the evening the evening meal should be omitted and no food given until the first roentgenogram is taken in the morning. At this time a fat meal is given and the roentgenogram taken one hour after the meal and, if desired, another three hours after the meal to determine the rapidity and characteristics of emptying. More satisfactory results are probably obtained if the injection is made in the morning with the stomach empty, omitting breakfast and lunch and taking roentgenograms four, eight and twenty-four hours after the injection. For gallbladder visualization alone the drug is administered orally: 4 Gm. in the form of plain gelatin capsules (8 capsules of 0.5 Gm. each), or dissolved in 30 cc. of distilled water and added to 120 to 240 cc. of grape juice, to be taken during and

after the evening meal, which should be of the usual amount but free of fat (the aqueous solution of the drug should not be more than 48 hours old). Meticulous roentgen ray technic is necessary, and if the interpretation of the cholecystogram is in question a check determination should be made either by the oral or, if preferred, by the intravenous method. The liver function test cannot be made by this method because the dye is not absorbed rapidly enough into the blood.

To make the determination of liver function, blood is collected one-half hour and again preferably one hour after the intravenous injection. The serum is alkalinized with a small drop of 5 per cent solution of sodium hydroxide and compared to a set of standard solutions as suggested by Rosenthal (An Improved Method for Using Phenoltetrachlorophthalein as a Liver Function Test, *J. Pharmacol. & Exper. Therap.* 19: 385 [June] 1922) and modified by Cole, Copher and Graham (Simultaneous Cholecystography and Determination of Liver Function, *J. A. M. A.* 90: 111 [April 7] 1928).

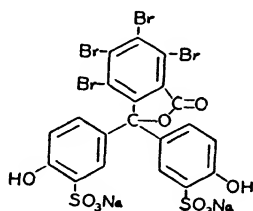
#### MALLINCKRODT CHEMICAL WORKS

**Iso-Iodeikon (Granules):** Bulk.

**Iso-Iodeikon (Granules):** 2.5 Gm. ampuls.

U. S. trademark 213,690.

**SULFOBROMOPHTHALEIN SODIUM-U. S. P.—**  
**Bromsulphalein Sodium-H. W. & D.—**Disodium phenoltetrabromophthalein sulfonate.—The disodium salt formed by the interaction of tetrabromophthalic acid (or anhydride) and phenol with subsequent sulfonation. It contains from 37 to 38 per cent of bromine. The structural formula may be represented as follows:



For standards, see the U. S. Pharmacopeia under SulFOBROMOPHTHALEIN Sodium and SulFOBROMOPHTHALEIN Sodium Injection.

**Actions and Uses.**—SulFOBROMOPHTHALEIN sodium is used intravenously in 5 per cent solution as a test of liver function. Normally, it is rapidly removed from the blood stream by the liver (excreted in the bile); the time required for its removal is dependent on the size of the dose and the functional capacity of the liver. Test doses of 2 mg. or 5 mg. of the drug per



kilogram of body weight are normally completely removed from the blood at the end of 20 and 45 minutes respectively. In hepatic disease, the dye is removed much more slowly and considerable amounts may remain in the blood for three hours or longer. The per cent of the dye retained in the blood at various intervals after its injection is measured colorimetrically by comparison with a set of suitably prepared standards, depending on the size of the test dose used.

Sulfobromophthalein sodium normally appears in the urine in traces only or not at all, but because of its possible retention in hepatic dysfunction, it may interfere with the use of the dye, phenolsulfonphthalein, as a test of kidney function, so that at least 24 hours should elapse before the latter test is performed, when the former has been used as a test of liver function.

Care must be taken to avoid injection outside the vein, since this not only interferes with the quantitative measurement of dye retention at the end of a given interval, but may be irritant to the tissues. Reactions to the compound itself are rare, but have occurred, especially with the use of the 5 mg. dose in obese patients.

*Dosage.*—The official intravenous dose of 2 mg. per kilogram of body weight as originally recommended for estimation of dye retention at the end of 30 minutes has been superseded by the use of 5 mg. per Kg. (1 cc. of the 5 per cent solution for each 10 Kg. or 22 pounds of body weight) and estimation of the dye in the blood at the end of 1 hour. The time intervals after injection for estimation of dye retention are perhaps better fixed according to the normal periods for total clearance of these doses, 20 and 45 minutes respectively. The 5 mg. dose is considered to give more sensitive results, so that the normal amount of dye retained in the blood, one hour after its administration is less than 6 per cent. Impairment of liver function will show a retention of dye from 6 to 40 per cent or more.

HYNSON, WESTCOTT & DUNNING, INC.

**Bromsulphalein, Sodium (Powder):** bulk.

**Solution Bromsulphalein Sodium 5% :** 3 cc. ampuls.

U. S. trademark 373,899 (Dec. 26, 1939).

### *Toxins for Immunity Tests*

(See Chapter on Serums and Vaccines, Diagnostic Agents.)

### *Allergenic Extracts Diagnostic*

(See Chapter on Allergenic Preparations.)

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## CHAPTER XIII

# Diuretics

### Mercury Compounds

The principal mercury diuretics are quite similar in structure; all are essentially methoxy-oxymercuripropylamides or dibasic acids. It appears established that the diuretic efficiency of these compounds is increased by the addition of theophylline, and at present all mercury diuretics are made available in combination with theophylline.

Acid-producing diuretics such as ammonium chloride administered orally prior to injection of the mercurials have been shown to increase the diuretic effect of the latter.

The reported fatalities following injection of mercury diuretics have all occurred after intravenous administration. Since these diuretics are effective and relatively safe when administered by intramuscular injection, this appears to be the route of choice.

Mercury diuretics are proposed for use in cardiac edema; nephrotic edema; ascites of liver disease; and in carefully selected cases of subacute and chronic forms of nephritis. The diuresis from the mercurials not only eliminates water, but also causes the elimination of sodium which diminishes the ability of the body to retain fluid. They are contraindicated in acute nephritis and in chronic kidney disease in which well defined tubular and glomerular changes are present.

Since mercury is known to give rise in sensitive patients to side effects such as stomatitis, gastric disturbances, vertigo, febrile reactions, and cutaneous eruptions, it is suggested that initial tests and careful regulation of dosage be followed when mercury diuretics are used. It should be recognized, however, that some patients may be sensitive to one mercurial, yet tolerate another satisfactorily. Demonstrated sensitivity to one mercurial is not necessarily proof that all mercury diuretics are contraindicated.

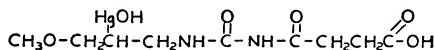
During prolonged administration of mercurial diuretics the urine should be examined periodically for albumin, casts and blood cells.

Repeated injections at intervals regulated to maintain freedom from cardiac edema based on changes in body weight have been recommended. In the absence of a diuretic response, repeated injections are contraindicated.

**MERALLURIDE.** — Mercuhydrin-Lakeside. — 1-(Methoxy-oxymercuripropyl)-3 succinyl urea.—Mercurated allylsuccinyl urea.—A mercurial compound derived from equimolecu-

lar quantities of mercurated allylsuccinylurea and theophylline. —Meralluride contains not less than 31.0 per cent and not more than 33.0 per cent of mercury, when dried over sulfuric acid for twenty-four hours.

The structural formula may be represented as follows:

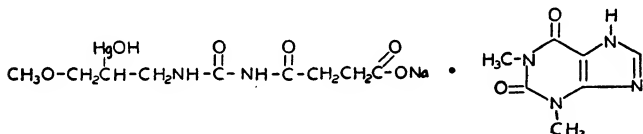


For tests and standards, see Section B.

*Actions and Uses.*—See Meralluride Sodium Solution.

*Dosage.*—See Meralluride Sodium Solution.

**MERALLURIDE SODIUM SOLUTION.** — **Mercuryhydrin Sodium Solution-Lakeside.**—A sterile aqueous solution containing in each cubic centimeter approximately 119 mg. of meralluride and 13 mg. of theophylline, adjusted with sodium hydroxide to a  $p_{\text{H}}$  of about 7.5. Each 1 cc. of meralluride sodium solution contains the equivalent of 39 mg. of mercury and 48 mg. of theophylline-U. S. P. The structural formula of meralluride sodium may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Meralluride sodium solution is a mercurial diuretic proposed for use in the edema of cardiorenal disease and of nephrosis, ascites of liver disease and other conditions in which a mercurial diuretic may be indicated.

It is well tolerated systemically and seldom causes pain at the site of injection when given intramuscularly. It is rapidly absorbed following intramuscular injection. It also is administered by intravenous injection.

The drug is contraindicated in acute nephritis and chronic kidney disease in which well defined tubular and glomerular changes are present. Since mercury is known to give rise in sensitive patients to side effects such as stomatitis, gastric disturbance, vertigo, febrile reaction and cutaneous eruptions, it is suggested that initial tests and careful regulation of dosage be followed when mercurial diuretics are used. During prolonged administration the urine should be examined periodically for albumin casts and blood cells.

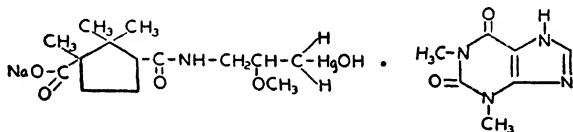
*Dosage.*—Depending on the condition of the patient and route and the frequency of administration, the usual dose of meralluride sodium solution is from 1 cc. to 2 cc. In view of occasional

cases of idiosyncrasy to mercurials, the initial dose could be 0.5 cc. or less. Subsequent injections may be given twice weekly, as indicated by the condition of the patient. One investigator has recommended smaller doses repeated at shorter intervals and emphasizes the importance of observing daily water balance instead of weekly observations.

LAKESIDE LABORATORIES, INC.

**Solution Mercuhydrin Sodium:** 1 cc. and 2 cc. ampuls.

**MERCUROPHYLLINE INJECTION-U. S. P.—Mer-cuzanthin-Campbell Products.**—"A sterile solution in water for injection of the sodium salt of  $\beta$ -methoxy- $\gamma$ -hydroxymercuri propylamide of trimethyl cyclopentane dicarboxylic acid ( $C_{14}H_{24}NO_5HgNa$ ) (the mercuri compound) and of theophylline in approximately molecular proportions. It contains an amount of mercury (Hg) equivalent to not less than 37 per cent and not more than 42 per cent of the labeled amount of the mercury compound, and theophylline equivalent to not less than 93 per cent and not more than 107 per cent of the labeled amount of theophylline ( $C_7H_8N_4O_2 \cdot H_2O$ )."—U. S. P.—The structural formula of mercurophylline injection may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Mercurophylline Injection.

**Actions and Uses.**—Mercurophylline injection is a potent diuretic. It is perhaps less toxic and more active than the purine-free mercurial diuretics. It has been demonstrated that when theophylline is combined with the mercurial, sloughs and venous thromboses occur with less frequency and severity. Clinical experiments suggested that the presence of theophylline enhances the rate and completeness of absorption, so that the drug is effective and well tolerated by intramuscular as well as intravenous administration. Studies by a number of investigators give indication that mercurophylline injection is an efficient diuretic. Supplementary administration of acidic salts, such as ammonium chloride, tends to increase the diuresis.

Mercurophylline injection is used to remove excess fluid\* in edema of congestive heart failure, nephrosis, and cirrhosis of the liver with ascites. It is contraindicated in advanced chronic nephritis and acute renal disease. Care should be taken not to restrict the intake of sodium chloride too drastically, as copious diuresis may give rise to the symptoms associated with hypochloremia. This effect can probably be overcome by using

ammonium chloride while allowing the benefits of sodium depletion. Mercurophylline is also available in tablet form.

**Dosage.**—Intramuscularly an amount equivalent to 0.1 Gm. of the mercury compound and 40 mg. of theophylline monohydrate. Care should be taken to prevent leakage into the subcutaneous tissue. If it is desired to determine if the patient may have intolerance to the compound a much smaller dose should be injected for trial. Mercurophylline injection is supplied in a concentration of 10 per cent (weight/volume) with respect to the sodium salt of the mercurated organic acid and 3.88 per cent with respect to theophylline monohydrate. Each cubic centimeter of mercurophylline injection represents 39 mg. of mercury in nonionizable form.

When maximum diuresis is desired in patients with massive edema, approximately 275 mg. administered at one time will usually produce a response comparable to that obtained with repeated injections. In severe cases, reaccumulation of the dropsical fluid may be partly or entirely controlled with 60 mg. to 110 mg. daily, while in milder cases with occult edema 60 mg. to 110 mg., three times daily, on two or three successive days is recommended for the relief of subjective symptoms of cardiac failure, notably dyspnea. The diuretic effect may be enhanced by ammonium chloride, 5 to 7.5 Gm., by mouth on the day preceding administration of the tablets.

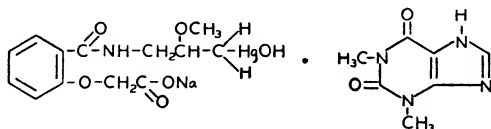
CAMPBELL PRODUCTS, INC.

**Solution Mercuzanthin:** 1 cc. and 2 cc. ampuls.

**Enteric Coated Tablets Mercuzanthin:** Each enteric coated tablet contains a concentrate representing 0.74 cc. of mercurophylline injection-U. S. P. equivalent to 30 mg. of mercury and 27 mg. of anhydrous theophylline.

U. S. patent 2,117,901. U. S. trademark 418,384.

**MERSALYL AND THEOPHYLLINE-U. S. P.**—**Salysgan-Theophyllin-Winthrop-Stearns.**—A mixture containing two parts by weight of mersalyl-U. S. P. (sodium [*ortho*(hydroxymercurimethoxypropylcarbonyl)phenoxy] acetate — for formula, see below) and one part by weight of theophylline.—U. S. P. The structural formula of mersalyl and theophylline may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Mersalyl and Theophylline Injection.

**Actions and Uses.**—Mersalyl and theophylline has been dem-

onstrated to produce less local reaction on intramuscular or intravenous injection than mersalyl alone and to be somewhat more effective. It is believed that the more rapid resorption of mersalyl in combination with theophylline accelerates diuresis and, by preventing the deposition of mercury, improves the local tolerance. Mersalyl and theophylline is proposed as a diuretic for dropsy in cardiorenal disease and in nephrosis, ascites of liver diseases and other conditions. It is contraindicated in acute nephritis and chronic kidney disease in an advanced stage with marked tubular and glomerular changes; also intestinal inflammation with diarrhea. As do other mercurials, mersalyl and theophylline may give rise to side effects, particularly stomatitis, gastric disturbance, more or less diarrhea, vertigo, headache, febrile reaction and cutaneous eruptions. When the use of mersalyl and theophylline is continued over a prolonged period of time the urine should be examined from time to time for albumin, casts and blood cells. Sudden fatalities have been reported following the use of mercurial diuretics injected intravenously and while these mishaps are very rare compared to the number of times these drugs are used caution should be exercised. Since the available evidence is in favor of ventricular arrhythmia as the mechanism of these fatalities, especial precautions should be exercised in patients who already are candidates for such arrhythmia, for example, patients with frequent ventricular beats, heavily digitalized patients, or those with recent myocardial infarction.

*Dosage.*—For Adults: Intramuscularly or intravenously mersalyl, 0.2 Gm. and theophylline, 0.1 Gm. For susceptibility, test the patient with one-half of the recommended dose. If well tolerated, the recommended dose may be given on the following day. In some cases this may have to be doubled for the full effect. Usually injections are not given more frequently than every three or four days. After relief of the dropsy, recurrences can often be prevented by occasional injections. One dose of about 0.3 Gm. may be given in the morning after breakfast and repeated in four to five days if required. As an adjunct to intravenous medication, about 0.1 Gm. may be given daily for one or two weeks but in such instances rest periods of one or two weeks should intervene between courses of treatment. For Children: The above recommendations should be reduced by one-half.

WINTHROP-STEARNs, INC.

**Solution Salyrgan-Theophylline:** 1 cc. and 2 cc. ampuls. Each cubic centimeter represents Mersalyl and Theophylline Injection U. S. P.

**Enteric Tablets Salyrgan-Theophylline:** Each tablet contains 80 mg. mersalyl and 40 mg. theophylline and is coated with shellac.

U. S. patent 2,213,457 (Sept. 3, 1940; expires 1957). U. S. trademark 188,515.

**MERSALYL AND THEOPHYLLINE INJECTION.**  
**U. S. P.**—Solution Salyrgan-Theophylline-Winthrop-Stearns.—“A sterile solution in water for injection of approximately 10 parts by weight of mersalyl  $C_{13}H_{16}HgNO_6Na$ ) to each 5 parts by weight of theophylline ( $C_7H_8N_4O_2 \cdot H_2O$ ). It contains mercury (Hg) equivalent to not less than 37 per cent and not more than 42 per cent of the labeled amount of ( $C_{13}H_{16}HgNO_6Na$ ) and not less than 93 per cent and not more than 107 per cent of the labeled amount of ( $C_7H_8N_4O_2 \cdot H_2O$ ).”—  
**U. S. P.**

For description and standards see Mersalyl and Theophylline Injection in the U. S. Pharmacopeia.

*Actions and Uses.*—See monograph on Mersalyl and Theophylline.

*Dosage.*—See monograph on Mersalyl and Theophylline.

## Urea

**UREA-U. S. P.**—Carbamide. Its structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Urea.

*Actions and Uses.*—Urea is an active diuretic: it is rapidly eliminated and is not poisonous. It is useless in the treatment of tuberculosis, and has no important solvent action on urinary calculi. It may be employed when diuresis is indicated, though it appears irrational in any renal disease characterized by retention of nitrogen. Urea should not be used as a diuretic when there is impaired elimination. Concentrated solutions of urea dissolve protein readily, but have little action on healthy tissue; hence urea has been used for the removal of necrotic tissue in infected wounds, and for the removal of foul odors. Certain observers believe that even weak solutions stimulate granulation and hasten the healing of wounds.

*Dosage.*—From 0.5 to 4 Gm. Urea is given in solution, or it may be enclosed in cachets.

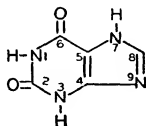
MALLINCKRODT CHEMICAL WORKS

**Urea (Crystals): Bulk.**

## Xanthine Derivatives

Caffeine, theobromine and theophylline are methyl xanthines, derived from xanthine by the introduction of two or three methyl radicals into a corresponding number of  $NH_2$  groups. As these

may occupy various positions in the xanthine nucleus, a considerable number of methyl xanthines exist, naturally or by synthesis, differing quantitatively in pharmacologic activity. Those named, however, are the only ones of therapeutic importance, namely, caffeine (1:3:7 trimethylxanthine); theobromine (3:7 dimethylxanthine), and theophylline (1:3 dimethylxanthine.)



Caffeine is usually obtained from tea or coffee; theobromine is obtained from cacao, or is made synthetically. Theophylline occurs in nature but in amounts too small to be commercially available. It is prepared synthetically. Theocin is a proprietary name for synthetic theophylline.

*Actions and Uses.*—Theobromine and theophylline surpass caffeine in their diuretic, and perhaps in cardiac and muscular actions. They are, therefore, generally preferred in cardiac edemas, etc., since they are equally, or more, effective, more prompt and largely avoid the unpleasant side effects (insomnia, nervousness, gastric disturbance) which often interfere with the use of caffeine in adequate doses. This freedom from side effects holds true, particularly for theobromine. Theophylline surpasses theobromine in diuretic efficacy, but its action is probably not so lasting; it may produce gastric disturbances; renal irritation has been reported. Theobromine is, therefore, generally preferred, sometimes preceded for a few days by theophylline. If central stimulation is desired, caffeine should be used. In recent years the xanthine derivatives have been used but seldom as diuretics as a result of the introduction of the more effective mercurial diuretics.

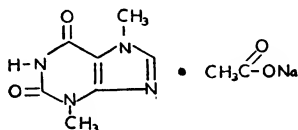
The slight solubility of theobromine and theophylline limits their usefulness. They are therefore used almost exclusively in the form of the readily soluble double salts (such as theobromine with sodium salicylate, U. S. P.), which they form with a considerable number of compounds. There is no reason to suppose that the particular salt used to procure the solubility has any material influence on the action. The dosage of these added compounds is also generally too small to produce therapeutic effects. It may, therefore, be assumed that the various preparations which have been introduced are strictly equivalent.

### *Theobromine Compounds*

**THEOBROMINE AND SODIUM ACETATE-U. S. P.**  
—“A hydrated mixture of theobromine sodium ( $C_7H_7N_4O_2Na$ ) and sodium acetate ( $NaC_2H_3O_2$ ) in approximately molecular



proportions. It yields not less than 55 per cent and not more than 65 per cent of theobromine ( $C_7H_8N_4O_2$ ).”—U. S. P. The structural formula may be represented as follows:



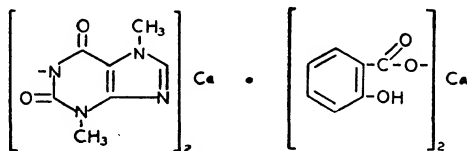
For description and standards see the U. S. Pharmacopeia under Theobromine and Sodium Acetate and Theobromine and Sodium Acetate Capsules.

*Actions and Uses.*—The uses of theobromine are similar to those of caffeine, but its action is said to be relatively greater on the heart and muscles and also as a diuretic. It does not act so powerfully on the central nervous system.

Theobromine sodium-acetate acts like theobromine over which it has the advantages of greater solubility and of being well tolerated by the stomach. While inferior in diuretic power to theophylline (which see), it is said to have greater power in sustaining the diuresis produced.

*Dosage.*—From 0.5 to 1 Gm., preferably in wafers or capsules. If in solution, this should be freshly prepared (with peppermint water), without sugar or mucilage.

**THEOBROMINE CALCIUM SALICYLATE**—**Theocalcin-Bilhuber-Knoll.**—A double salt or mixture of calcium theobromine ( $[C_7H_7O_2N_4]_2Ca$ ) and calcium salicylate ( $[C_7H_5O_3]_2Ca$ ). It contains not less than 44 per cent of theobromine. The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Theobromine calcium salicylate acts like theobromine, over which it has the advantage of greater solubility. It is, however, less soluble than theobromine with sodium salicylate; on this account it is claimed to be less likely to produce gastric irritation.

*Dosage.*—Average dose, from 0.5 to 1 Gm. three times a day.

BILHUBER-KNOLL CORP.

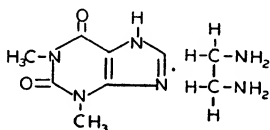
**Theocalcin (Powder):** bulk.

**Tablets Theocalcin:** 0.5 Gm.

U. S. patent 1,547,698 (July 28, 1925; expired). U. S. trademark 194,898.

### *Theophylline and Theophylline Compounds*

**AMINOPHYLLINE-U. S. P.**—Theophylline Ethylene-diamine.—“Contains not less than 75 per cent and not more than 82 per cent of anhydrous theophylline ( $C_7H_8N_4O_2$ ), and not less than 12.3 per cent and not more than 13.8 per cent of ethylenediamine ( $C_2H_4(NH_2)_2$ ).”—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Aminophylline, Aminophylline Injection and Aminophylline Tablets.

**Actions and Uses.**—Aminophylline has the actions and uses of theophylline and theophylline with sodium-acetate, over which it has the advantage of greater solubility. Like these it has a diuretic action, and the xanthine derivatives are useful diuretics in congestive heart failure. Used intravenously, aminophylline is often extremely effective in relieving the paroxysmal dyspnea or pulmonary edema of cardiac origin. The xanthines stimulate the myocardium to increased vigor of contraction. This is accompanied by increased cardiac output and increased work of the heart. Clinical evaluation of the usefulness of the xanthines in the treatment of coronary artery disease is far from satisfactory, and claims for such use do not appear acceptable in view of the existing evidence. Increased coronary blood flow produced by theophylline in the experimental animal follows, rather than precedes, the myocardial stimulation, and claims for the clinical use of this drug in increasing the blood supply to the heart are not acceptable until it can be shown that the increase in coronary flow is disproportionately large in comparison to the increase in cardiac metabolism. The xanthines are useful in the treatment of Cheyne-Stokes respiration. At times the effect is transient but in other cases the effect may last several hours. Aminophylline is effective in the treatment of bronchial asthma; it finds its greatest field of usefulness in patients who are not relieved by epinephrine. It is probably a safer drug than epinephrine in occasional cases where there may be indecision concerning the “bronchial” or “cardiac” nature of asthmatic attacks. In general it is less effective than epinephrine

and should not supplant the latter. There is no basis for claims that the xanthines effectively reduce high blood pressure. The available evidence is opposed to claims that these drugs are useful in the treatment of peripheral vascular disease.

**Dosage.**—Orally, from 0.1 to 0.5 Gm. three times daily depending on tolerance; by rectal administration in the form of suppositories, or, as a retention enema; intramuscularly, 0.5 Gm.; intravenously 0.25 Gm. to 0.5 Gm. When given intravenously, infusion should be performed slowly in order to avoid untoward effects.

AMERICAN PHARMACEUTICAL CO., INC.

**Suppositories Aminophylline:** 0.5 Gm. in a water miscible base which dissolves in body fluids under conditions of use.

**Tablets Aminophylline:** 0.1 Gm. and 0.195 Gm.

**Enteric Coated Tablets Aminophylline:** 0.2 Gm.

BARLOW-MANEY LABORATORIES, INC.

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm. and 0.1 Gm. and 0.2 Gm. enteric coated.

BARRY BIOLOGICAL LABORATORY, DIVISION OF BARRY LABORATORIES, INC.

**Solution Aminophylline:** 0.50 Gm. in 2 cc. and 20 cc. ampuls and 0.25 Gm. in 10 cc. ampuls.

ERNST BISCHOFF COMPANY, INC.

**Aminophylline (Powder):** bulk.

**Solution Aminophylline:** Ampuls 0.24 Gm. in 10 cc. and 0.48 Gm. in 2 cc. ampuls.

**Tablets Aminophylline:** 0.1 Gm.

GEORGE A. BREON & CO.

**Solution Aminophylline:** 0.25 Gm. 10 cc. and 0.5 Gm. 20 cc. ampuls.

**Solution Aminophylline with Benzyl Alcohol 2%:** 0.48 Gm. 2 cc. ampuls.

**Tablets Aminophylline:** 100 mg. and 200 mg.

BREWER & CO., INC.

**Solution Aminophylline:** 24 mg. in 10 cc. ampuls.

**Solution Aminophylline with Benzyl Alcohol 2%:** 48 mg. in 2 cc. ampuls.

BRISTOL LABORATORIES, INC.

**Solution Aminophylline:** 0.48 Gm. in 2 cc. and 0.24 Gm. in 10 cc. ampuls.

## COLE CHEMICAL COMPANY

**Tablets Aminophylline:** 0.1 Gm.

**Solution Aminophylline:** 0.5 Gm. in 2 cc. ampuls with benzyl alcohol 1.5 per cent.

## H. E. DUBIN LABORATORIES, INC.

**Aminophylline (Powder):** 15 Gm., 113 Gm., and 454 Gm. bottles.

**Solution Aminophylline:** 0.24 Gm. in 10 cc., 0.48 Gm. in 2 cc. and 0.48 Gm. in 20 cc. ampuls.

**Tablets Aminophylline:** 0.1 Gm., 0.2 Gm. and 0.2 Gm. enteric coated.

**Rectal Suppositories Aminophylline:** 0.36 Gm. and 0.5 Gm.

## ENDO PRODUCTS, INC.

**Tablets Aminophylline:** 0.1 Gm.

**Solution Aminophylline with Benzyl Alcohol 2%:** 0.48 Gm. in 2 cc. and 0.24 Gm. in 10 cc. ampuls.

## GANE AND INGRAM, INC.

**Aminophylline (Powder):** bulk.

## GOLD LEAF PHARMACAL CO.

**Solution Aminophylline:** 0.5 Gm. 2 cc. and 20 cc. ampuls and 0.25 Gm. 10 cc. ampuls.

## THE HARROWER LABORATORY, INC.

**Tablets Aminophylline:** 0.1 Gm.

## INGRAM LABORATORIES, INC.

**Solution Ingraloids Aminophylline:** 0.243 Gm. in 2 cc. or 10 cc. and 0.486 Gm. in 2 cc., 10 cc. or 20 cc. ampuls.

## KREMERS-URBAN CO.

**Solution Aminophylline with Benzyl Alcohol 2%:** 0.24 Gm. 10 cc. ampuls, 0.48 Gm. 2 cc. and 20 cc. ampuls.

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm.

## LAKESIDE LABORATORIES, INC.

**Solution Aminophylline:** Ampuls 0.24 Gm. in 10 cc. and 0.48 Gm. in 20 cc. ampuls.

**Tablets Aminophylline:** 0.1 Gm.

## LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Solution Aminophylline:** 0.25 Gm. in 10 cc. and 0.50 Gm. in 2 cc. ampuls.

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm.

LINCOLN LABORATORIES, INC.

**Solution Aminophylline:** 0.48 Gm. in 2 cc. and 20 cc. ampuls and 0.24 Gm. in 10 cc. ampuls.

S. E. MASSENGILL COMPANY

**Tablets Aminophylline:** 0.1 Gm. and 0.19 Gm.

MERCK & Co., INC.

**Theophylline Ethylenediamine (Powder):** 30 Gm., 124 Gm. and 498 Gm. bottles.

THE WM. S. MERRELL CO.

**Tablets Aminophylline:** 0.1 Gm.

THE WM. S. MERRELL CO., LOESER LABORATORY DIVISION

**Solution Aminophylline:** 0.45 Gm. in 2 cc. and 0.25 Gm. in 10 cc. ampuls.

E. S. MILLER LABORATORIES, INC.

**Solution Theophylline Ethylenediamine 2.4% :** 10 cc. and 20 cc. ampuls.

**Solution Aminophylline 24% W/V in Ethylenediamine Solution 1% V/V with Benzyl Alcohol 2% V/V:** 2 cc. ampuls.

**Tablets Theophylline Ethylenediamine:** 90 mg. and 180 mg.

PHARMEDIC CORPORATION

**Aminophylline (Powder):** bulk.

**Solution Aminophylline:** 0.24 Gm. in 10 cc. and 0.48 Gm. in 2 cc. ampuls.

**Suppositories Aminophylline:** 0.36 Gm.

**Tablets Aminophylline:** 0.1 Gm.

PREMO PHARMACEUTICAL LABORATORIES, INC.

**Aminophylline (Powder):** 28.35 Gm. and 113.39 Gm. bottles.

**Enerels Aminophylline:** 0.1 Gm. and 0.2 Gm. enteric coated.

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm.

**Solution Aminophylline:** 0.25 Gm. in 10 cc. and 0.5 Gm. in 2 cc. ampuls.

**Suppositories Aminophylline:** 0.5 Gm. in a water soluble Carbowax base.

## RAYMER PHARMACAL COMPANY

**Solution Aminophylline:** 0.26 Gm. in 10 cc. and 0.48 Gm. in 20 cc. ampuls.

**Solution Aminophylline with Benzyl Alcohol 2% :** 0.48 Gm. in 2 cc. ampuls.

**Suppositories Aminophylline:** 0.5 Gm.

**Tablets Aminophylline:** 97 mg. and 0.194 Gm.

**Enteric Coated Tablets Aminophylline:** 97 mg. and 0.194 Gm. Each tablet is enteric coated with a mixture of sandarac and phenyl salicylate.

## WILLIAM H. RORER, INC.

**Solution Aminophylline:** 0.24 Gm. 10 cc. ampuls.

## G. D. SEARLE &amp; CO.

**Aminophyllin (Powder):** bulk.

**Solution Aminophyllin:** 0.25 Gm. in 10 cc. and 0.5 Gm. in 20 cc. ampuls for intravenous injection.

**Solution Aminophyllin with Benzyl Alcohol 2% :** 0.5 Gm. in 2 cc. ampuls, with benzyl alcohol, 40 mg., for intramuscular injection.

**Tablets Aminophyllin:** 0.1 Gm. and 0.2 Gm. and 0.1 Gm. and 0.2 Gm. enteric coated.

**Suppositories Aminophyllin:** 0.50 Gm. Each suppository contains aminophyllin, 0.50 Gm. incorporated into a specially compounded wax base which will not liquefy in storage at temperatures up to 130 F. but which disintegrates readily under conditions of use.

## CARROLL DUNHAM SMITH PHARMACAL COMPANY

**Solution Aminophylline:** 0.25 Gm. in 10 cc. and 0.5 Gm. in 20 cc. ampuls.

**Solution Aminophylline with Benzyl Alcohol 2% :** 0.5 Gm. in 2 cc. ampuls.

**Tablet Aminophylline:** 0.1 Gm.

**Enteric Coated Tablets Aminophylline:** 0.2 Gm. enteric coated with shellac.

## SMITH-DORSEY COMPANY

**Solution Aminophylline:** 0.5 Gm. in 20 cc., 0.25 Gm. in 10 cc. and 0.5 Gm. in 2 cc. ampuls.

**Suppositories Aminophylline:** 0.5 Gm.

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm.

THE VALE CHEMICAL CO., INC.

**Enteric Coated Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm. Each tablet is enteric coated with a coating composed of white glaze, magnesium and calcium carbonate.

**Tablets Aminophylline:** 0.1 Gm.

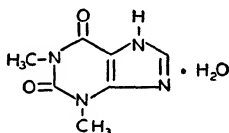
WARREN-TEED PRODUCTS COMPANY

**Tablets Aminophylline:** 0.1 Gm.

WYETH INCORPORATED

**Suppositories Aminophylline:** 0.5 Gm.

**THEOPHYLLINE-U. S. P. — Theocin - Winthrop-Stearns.**—The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Theophylline and Theophylline Tablets.

**Actions and Uses.**—Theophylline is used in cardiac affections, edemas, nephritis, etc. It has a diuretic action similar to that of caffeine or theobromine, but is more active and it is often effective when caffeine and theobromine are not. However, the diuretic response is not as lasting; for this reason, it is advisable to replace it after two or three days by theobromine. Theophylline may produce gastric and, perhaps, renal irritation.

**Dosage.**—0.25 Gm. three times daily.

MERCK & CO., INC.

**Theophylline (Crystals):** 30 Gm., 124 Gm. and 498 Gm. bottles.

E. S. MILLER LABORATORIES, INC.

**Tablets Theophylline:** 0.1 Gm.

WINTHROP-STEARNES, INC.

**Theocin (Powder):** bulk. Prepared synthetically.

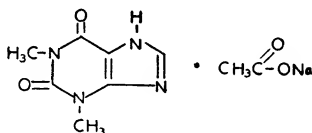
**Preparation.**—

Theocin is obtained by heating the monoformyl derivative of 1,3-dimethyl-4,5-diamido-2,6-dioxy-pyrimidine with alkalis resulting in the preliminary formation of an alkaline salt of the formyl compound. On further heating, this splits off one molecule of water, forming the alkali salt of theocin. Subsequent treatment with acids liberates theocin.

**Tablets Theocin: 0.1 Gm.**

U. S. patent 716,994 (Dec. 30, 1902; expired). U. S. trademark 39,135.

**THEOPHYLLINE AND SODIUM ACETATE.**  
**U. S. P.—Theocin Soluble-Winthrop-Stearns.**—"A hydrated mixture of theophylline sodium ( $C_7H_7N_4O_2Na$ ) and sodium acetate ( $NaC_2H_3O_2$ ) in approximately molecular proportion. It yields not less than 55 per cent and not more than 65 per cent of anhydrous theophylline ( $C_7H_8N_4O_2$ )."—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Theophylline and Sodium Acetate and Theophylline and Sodium Acetate Tablets.

**Actions and Uses.**—It has the actions and uses of theophylline, with the advantage of being much more soluble in water.

**Dosage.**—From 0.2 to 0.35 Gm., best given after meals.

WINTHROP-STEARNES, INC.

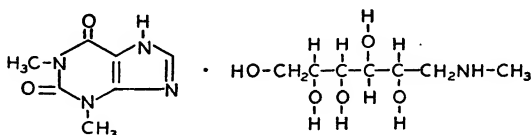
**Theocin Soluble (Powder):** bulk.

**Tablets Theocin Soluble: 0.16 Gm.**

U. S. patent 716,994 (Dec. 30, 1902; expired). U. S. trademark 39,135.

**THEOPHYLLINE-METHYLGLUCAMINE.**—**Gluco-**  
**phyllin-Abbott.**—An equimolecular mixture of theophylline-U. S. P. ( $C_7H_8N_4O_2 \cdot H_2O$ ) and methylglucamine ( $C_7H_{17}NO_5$ ). Dosage forms of theophylline-methylglucamine contain not less than 95 per cent nor more than 105 per cent of the labeled quantities of theophylline and methylglucamine.

The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Theophylline-methylglucamine is identical in action and therapeutic purpose to aminophylline (theophylline ethylenediamine) U. S. P. over which it has no advantage. It is



therefore similarly useful orally and by injection to produce the effects of theophylline when a more soluble salt than theophylline and sodium acetate is needed. It is employed orally as a diuretic and myocardial stimulant for pulmonary edema and paroxysmal dyspnea in congestive heart failure, and for the relief of Cheyne-Stokes respiration. It is also useful in the relief of acute bronchial asthma, particularly in patients who have become unresponsive to epinephrine. As with aminophylline, claims for its use in coronary or peripheral vascular disease and in hypertension are not recognized on the basis of available evidence.

*Dosage.*—Theophylline-methylglucamine represents about 50 per cent of theophylline, as compared to about 78 per cent contained in aminophylline U. S. P., so that the ratio of dosage to the latter is approximately 2:3. On this basis the dosage recommended for theophylline-methylglucamine should be about one and one-half times the dose ordinarily prescribed for aminophylline.

Orally from 0.15 to 0.75 Gm. three or four times daily after meals, given continuously for only a few days at a time with intervening rest periods of one or two days. Intramuscularly, 0.75 Gm. in 2 cc.; intravenously 0.36 to 0.75 Gm. in 10 cc. to 20 cc. As with aminophylline, intravenous injection should be made slowly to avoid untoward effects.

#### ABBOTT LABORATORIES

**Solution Glucophyllin:** 0.366 Gm. in 10 cc. ampuls.

**Solution Glucophyllin:** 0.732 Gm. in 2 cc. and 20 cc. ampuls.

**Enterab Tablets Glucophyllin:** 0.152 Gm. Each tablet is enteric coated with a resin prepared from stearic acid, phthalic anhydride and glucerine.

**Tablets Glucophyllin:** 0.152 Gm. and 0.304 Gm.

U. S. patent 2,161,114 (June 6, 1939; expires 1956). U. S. trademark 334,367.

## CHAPTER XIV

# Oxytocics

Ergot, the dried sclerotium of *Claviceps purpurea* developed on rye, contains a number of specific alkaloids to which it owes its therapeutic effects. In addition, a great variety of chemical substances have been isolated from the crude drug. These include carbohydrates, lipoids, dyes, amino acids, and a number of biogenous amines. Of the last group may be mentioned histamine, tyramine, and acetylcholine, substances which are pharmacologically active but which play a negligible role in the therapeutic effect of the drug.

The alkaloids thus far isolated consist of several pairs of optical isomers, one member of each pair being pharmacologically potent and the other member almost inert. The members of each pair may be interconverted by chemical procedures, and it has been suggested that the inert alkaloids may be formed to some extent from the active ones in the process of extraction.

The isomeric pairs of alkaloids may be listed as follows:

Potent	Relatively Inactive	Formula
1. Ergotoxine	Ergotinine $\Psi$ Ergotinine	$C_{35}H_{39}O_5N_5$
2. Ergotamine	Ergotaminine	$C_{38}H_{35}O_5N_5$
3. Ergosine	Ergosinine	$C_{30}H_{37}O_5N_5$
4. Ergocristine	Ergocristinine	$C_{35}H_{39}O_5N_5$
5. Ergonovine	Ergometrinine	$C_{19}H_{23}O_2N_3$

It may be noted that the first of the five groups consists of three rather than of two members, and furthermore that the ergotoxine and ergocristine groups are isomeric with each other. It is also striking that the molecular size of ergonovine is definitely less than that of the other alkaloids. The inert alkaloids in solution in chloroform show a high degree of dextro-rotation, while the active alkaloids are levorotatory, ergonovine showing a much smaller degree of levorotation than the others.

Various molecular complexes consisting of a potent and an inert alkaloid have also been isolated. These may show a pharmacologic activity somewhat different from the average of those of its components. In this group may be mentioned sensibamine (ergotamine plus ergotaminine) and ergoclivine (ergosine plus ergosinine).

Common to all of the above alkaloids is a hydrolysis product, lysergic acid ( $C_{16}H_{16}O_2N_2$ ), which contains an indole group. Isomerism in the lysergic acid part of the molecule is believed to account for differences in members of the same pair. The various pairs of alkaloids differ in the other products of hydrolysis, which are unique in the field of alkaloidal chemistry in

that certain of them are amino acids. These groups undoubtedly determine the variations in pharmacologic action shown by the active alkaloids of different pairs, e. g., ergotoxine and ergonovine.

Ergotoxine may be crystallized from benzene, carbon bisulfide and acetone. It is insoluble in water and light petroleum, sparingly soluble in ether, and very soluble in methyl and ethyl alcohol, chloroform, acetone and ethyl acetate. The phosphate of ergotoxine is soluble in 313 parts of water at room temperature; the ethanesulfonate is sparingly soluble in water, somewhat more soluble in ethyl alcohol, and dissolves readily in methyl alcohol. Ergotinine is insoluble in water, sparingly soluble in ethyl alcohol, and very readily soluble in chloroform.

Ergotamine crystallizes from aqueous acetone, methyl alcohol, ethyl alcohol and benzene. It is insoluble in water and less soluble than ergotoxine in benzene, chloroform and ether, but is readily soluble in nitrobenzene, pyridine and dilute sodium hydroxide. It forms a tartrate, a methanesulfonate, and a phosphate, all of which are water soluble. Ergotamine is fairly soluble in chloroform and in nitrobenzene, and readily soluble in pyridine. It is much less soluble than ergotamine in other solvents from which it crystallizes relatively solvent-free, unlike most of the ergot alkaloids which tend to retain solvent of crystallization.

Ergonovine may be crystallized from a number of solvents, possibly most readily from benzene and chloroform. In contrast to the other alkaloids it is appreciably soluble in water and comparatively insoluble in chloroform. It forms many crystalline salts which are markedly soluble in water. Ergonovine is more basic than the other alkaloids and less readily precipitated by Mayer's reagent. It is present in aqueous and alcoholic extracts of those ergots which contain it, unlike ergotoxine and ergotamine, which are extracted by alcohol but not by water. The content of ergonovine is not constant in specimens of ergot from different localities and may even vary in specimens from the same locality. It occurs in lower concentrations (up to 0.2 mg. per Gm. of ergot) than does the ergotoxine-ergotamine group, which may reach 2 mg. per Gm. of ergot. Ergometrinine is even more basic than ergonovine, much more soluble in chloroform, only slightly soluble in water, and may be crystallized from acetone. It forms crystalline salts unlike the other alkaloids of the inert series.

*Pharmacology.*—Ergotoxine, ergotamine, ergosine, and presumably ergocristine show essentially the same type of pharmacologic action although certain individual variations have been observed.

They cause a moderate and prolonged increase in tone and rhythmic contractions of the uterus by direct stimulation of smooth muscle. The blood pressure is increased in the same way, by arteriolar constriction. The effect of epinephrine on the blood pressure may be lessened or reversed through paralysis of the effector responses of the sympathetic nervous system. In suffi-

cient dosage cyanosis of the cockscomb and with toxic doses gangrene through vascular occlusion are caused by direct injury to capillary endothelium, and by persistent vasospasm. Gangrene may also appear clinically on administration of toxic doses. The inhibition of ephedrine action by ergot alkaloids may also be demonstrated on other smooth muscle organs, more readily on those to which the sympathetic nerve supply is predominantly motor, such as the rabbit uterus. Poisonous doses in the intact animal produce acute manifestations essentially due to central stimulation consisting of excitement, tremor, weakness, pyrexia, vomiting and convulsions.

Ergotoxine shows slightly greater activity than ergotamine in inhibiting the action of epinephrine on isolated tissues. Ergosine is probably even more potent than ergotoxine in this regard. Ergotamine is only about two-thirds as toxic to white mice as ergotoxine.

Ergonovine is effective on the uterus in smaller doses and concentrations than are the other alkaloids. This difference is particularly apparent in the puerperal state when the uterus is especially sensitive to ergonovine. The uterine action is the only appreciable effect of moderate doses of ergonovine, unpleasant side actions being rarely encountered clinically. The promptness of the uterine action, in comparison with that produced by ergotoxine and ergotamine, is an outstanding clinical feature; also it is much more effective when administered by mouth than are the latter alkaloids. It increases both the tone and the rate and amplitude of rhythmic contractions of the uterus, the latter effects probably being proportionately greater than the tonus changes. The duration of effect, although probably less than that of ergotoxine and ergotamine, is at least comparable with that of these alkaloids. The circulatory effects which are referable to actions on the central nervous system and peripheral vascular mechanism vary with the animal and with experimental conditions. A slight increase in blood pressure may be encountered clinically. Ergonovine shows a definite sympathomimetic effect and little or no inhibition of epinephrine action. Although it produces the characteristic cockscomb reaction, it shows definitely less tendency to produce gangrene than ergotoxine and ergotamine. It is less toxic than these two alkaloids, but in poisonous doses produces similar effects.

*Assay.*—All ergot preparations, especially those containing water, deteriorate with age. It is necessary therefore to standardize them, and the date of assay should be indicated on the container.

Ergot is assayed officially in this country by the cockscomb method (see U. S. P. XII), which measures the total pharmacologically active alkaloids. Various physical and chemical methods which measure the total alkaloidal content have also been employed. Of this group, the colorimetric method, which utilizes the blue coloration produced by p-dimethylaminobenzaldehyde with the alkaloids and dependent on the indole group of the lysergic acid component, has been extensively used. Such methods

do not distinguish between ergonovine and the ergotoxine-ergotamine group, and consequently are not a true measure of the pharmacologic potency unless a constant proportion of these groups in various ergots could be assumed. To overcome this difficulty, assays involving a previous separation of the two groups have been proposed. The Broom-Clark method, which is based on the inhibition of the action of epinephrine on the isolated rabbit uterus, does not assay ergonovine, which lacks this particular action.

**ERGOT ASEPTIC.**—A liquid extract of ergot, standardized by the cockscomb method of assay to have the same potency as fluidextract of ergot. U. S. P.

*Actions and Uses.*—The several active principles of ergot have actions that differ somewhat, and the combined effect is utilized in ergot. The action of histamine and tyramine in ergot is probably negligible, and only the alkaloids exert a prolonged effect on the human uterus when ergot is used clinically.

Ergot causes powerful tonic, sometimes tetanic, contractions of the uterus. It also produces contractions of other involuntary muscles such as those of the blood vessels, bladder, stomach and intestines. Extreme and long-continued contraction of the blood vessels, especially of those of the extremities, may lead to gangrene with resultant damage to capillary endothelium as the final cause of the vascular occlusion from ergotism.

The principal use of ergot is to prevent postpartum hemorrhage. For this purpose a full dose is sometimes given as soon as the second stage of labor terminates, but it should not be given until the placenta has been expelled. Its use during labor should be avoided, as it may cause rupture of the uterus or asphyxia of the child. It is employed as a prophylactic for "after-pains." Ergot is also used for hemorrhage from the uterus in menorrhagia and metorrhagia. Its use for hemorrhage from other internal organs is not rational.

*Dosage.*—1 to 2 cc. Ergot aseptic is intended for intramuscular injection. Ergot aseptic is marketed in ampules only. The date of manufacture appears on each package and the product is not guaranteed to possess its full potency for more than one year from time of manufacture.

*Preparation.*—

Ergot is extracted with diluted alcohol acidulated with hydrochloric acid. The percolate is partially neutralized with alkali and concentrated by distillation in a partial vacuum at a temperature not above 80 C. A large excess of alcohol is added to the concentrated percolate and the material which precipitates is removed. The liquid portion is freed from alcohol by distillation in a partial vacuum at a low temperature, and chlorobutanol in the proportion of 0.005 Gm. per cc. added to the aqueous slightly acid liquid. After three weeks the liquid is assayed, adjusted to proper volume and sealed in ampules. The finished ampules are tested for sterility and potency.

Ergot aseptic is standardized to the same potency as fluidextract of ergot-U. S. P., as determined by the cockscomb method described in the U. S. P. XII.

PARKE, DAVIS & COMPANY

**Ampoule Ergot Aseptic: 1 cc.**

**ERGOTAMINE TARTRATE-U. S. P.—Gynergen-Sandoz.**—"The tartrate of an alkaloid obtained from ergot."  
*U. S. P.*

For description and standards see the U. S. Pharmacopeia under Ergotamine Tartrate and Ergotamine Tartrate Tablets.

*Actions and Uses.*—Ergotamine tartrate stimulates smooth muscle thus causing an increase in blood pressure, contraction of the uterus, etc. (the isolated uterus of the guinea pig is affected in dilutions of from 1 in 150,000,000 to 1 in 200,000,000). In large doses it paralyzes the cellular response to the effector fibers of the sympathetic nervous system. It causes the darkening of the coxcomb characteristic of the action of ergot and in toxic doses causes gangrene and convulsions. There is evidence that ergotamine tartrate relieves the pain and shortens the attack in many cases of migraine. However, before relief occurs, nausea and vomiting may be increased. The drug should not be used as a prophylactic. Caution in its use is advisable on account of the danger of poisoning from long continued use or overdosage.

Ergotamine tartrate may be used when the action of ergot to produce uterine contraction is desired; it is contraindicated whenever tonic contraction of the uterus would be dangerous. Ergotamine tartrate is also stated to be indicated in hemorrhage following abortion, after curettage and in postpartum endometritis.

*Dosage.*—Intramuscularly, the average dose is 0.25 mg.; orally, 1 mg. two to four times daily. Caution should be exercised in the repeated use of ergotamine; cases of gangrene have been reported where the use of the alkaloid has been continued over a period of some days. For migraine the dose recommended is 0.25 mg. by subcutaneous injection, to be followed in two or three hours by a full dose of 0.5 mg. if no untoward effects have been seen or if the original dose has not been effective. If preferred, two or three tablets containing 1 mg. each may be given sublingually or by ingestion to be repeated hourly up to 8 or 9 tablets, but this method of administration is not so effective as when the drug is given by the subcutaneous route.

SANDOZ CHEMICAL WORKS, INC.

**Solution Gynergen:** ampuls 0.5 cc. and 1 cc. Each cc. contains 0.5 mg. of ergotamine tartrate and a small excess of tartaric acid; 15 cc. and 100 cc. bottles. Each cc. contains 1 mg. of ergotamine tartrate and a small excess of tartaric acid.

**Tablets Gynergen:** 1 mg.

U. S. patent 1,394,233 (Oct. 18, 1921; expired); 1,435,187 (Nov. 14, 1922; expired). U. S. trademark 173,047.

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## CHAPTER XV

# Gastrointestinal Drugs

The class of drugs affecting the motor and secretory activities of the gastro-intestinal tract is very large. The present chapter includes only antacids, cholagogues, emollients and laxatives. Certain other drugs that have marked effects on the secretions and movements of the gastro-intestinal tract will be found in the chapter on Autonomic Drugs.

### Antacids

**ALUMINUM HYDROXIDE GEL-N. N. R.—Creamalin-Winthrop-Stearns.**—An aqueous suspension containing not less than 3 per cent nor more than 4.4 per cent of aluminum oxide, chiefly in the form of aluminum hydroxide. Flavoring, sweetening and preservatives may be added.

See also standards of the U. S. Pharmacopeia under Aluminum Hydroxide Gel.

For tests and standards, see Section B.

*Actions and Uses.*—Aluminum hydroxide gel has been shown to be an effective gastric antacid neutralizing hydrochloric acid of the stomach by chemical reaction. It does not increase the  $pH$  of the gastric juice beyond the point which interferes with peptic digestion, does not stimulate a compensatory increase in free gastric acidity and does not produce systemic alkalization, which are the principal disadvantages of soluble basic salts. The amphoteric nature of aluminum hydroxide gel is not of clinical significance because it reacts as an acid only in fluids with a  $pH$  above 9: such a  $pH$  is not encountered in the gastro-intestinal tract. Its so-called buffer action occurs only at a  $pH$  of about 4. It is presumed that the acid salt aluminum chloride, which is formed by the reaction of aluminum hydroxide with hydrochloric acid in the stomach, is reconverted to the original compound or other aluminum compounds by reaction with the less acid contents of the small intestine, and the chloride is reabsorbed. Its mild astringent and demulcent properties are believed to be of some importance in the local effect on peptic ulcer. Some evidence also suggests that its effectiveness may be further explained by the tendency to increase mucin secretion and the ability to precipitate pepsin in vitro.

As with other aluminum compounds, aluminum hydroxide is not absorbed from the gastro-intestinal tract to any appreciable extent and is therefore nontoxic when administered orally. Its astringent property may produce a constipating effect.

There is evidence available to suggest that administration of excessive amounts of aluminum compounds may interfere with the absorption of certain minerals and can produce a phosphorus deficiency. This objection does not affect the use of ordinary doses employed in peptic ulcer and gastric hyperacidity, and the diet employed in these conditions is ordinarily relatively rich in phosphorus. Aluminum hydroxide gel may possess adsorptive properties, but specific conclusive evidence that acid, toxins, bacteria or gases are absorbed is lacking, and in the case of hydrochloric acid is opposed by *in vitro* evidence to demonstrate that its reaction with this substance is completely accounted for on the basis of simple chemical neutralization.

Aluminum hydroxide gel is recognized for oral use as an adjunct in the treatment of peptic ulcer (gastric and duodenal) to promote healing, relieve pain and control hemorrhage in this condition and for the control of gastric hyperacidity when this can be recognized as a cause of distress. Its oral or rectal use in the treatment of other gastro-intestinal conditions is not adequately supported by existing clinical evidence.

**Dosage.**—Aluminum hydroxide gel is administered orally in doses of from 4 to 8 cc. in one-half glass of water or milk every two or four hours, or one-half to one hour after meals. It may be administered by the method of continuous drip by stomach tube in dilutions of 1 part to 2 or 3 parts of water (25 to 33½ per cent aluminum hydroxide gel) at the rate of 15 to 20 drops a minute for a total of approximately 1,500 cc. of diluted suspension per 24 hours.

#### BARLOW-MANEY LABORATORIES

**Gel Aluminum Hydroxide:** 480 cc. bottles. Contains the equivalent of 3.6 to 4.4 per cent of aluminum oxide (U. S. P. XII).

#### MACALLISTER LABORATORY

**Gel Aluminum Hydroxide:** 480 cc. and 3.84 liter bottles. Contains 4.6 per cent aluminum hydroxide (equivalent to 3.0 per cent aluminum oxide) with saccharin sodium-U. S. P. and oil of peppermint-U. S. P. as flavoring agents.

#### THE RESERVE RESEARCH Co.

**Gel Aluminum Hydroxide:** 360 cc. bottles. Contains 5.5 per cent of aluminum hydroxide (equivalent to 3.6 per cent of aluminum oxide) and, as a flavoring agent, oil of peppermint.

#### WILLIAM H. RORER, INC.

**Gel Aluminum Hydroxide:** 355 cc. and 3.79 liter bottles. Contains the equivalent of 3.6 to 4.4 per cent of aluminum oxide.

#### SCHIEFFELIN & Co.

**Gel Aluminum Hydroxide:** Contains 5.5 per cent aluminum hydroxide (equivalent to 3.6 per cent aluminum oxide). Sac-



charin and Oil of Peppermint U. S. P. are added as flavoring agents. Marketed in bottles of 480 cc. and 3.84 liters.

THE UPJOHN COMPANY

**Gel Aluminum Hydroxide:** 240 cc. and 3,840 cc. bottles. Contains the equivalent of 3.6 to 4.4 per cent of aluminum oxide (U. S. P. XII).

WINTHROP-STEARNs, INC.

**Creamalin:** Contains 5.5 per cent aluminum hydroxide (equivalent to 3.6 per cent aluminum oxide). Oil of peppermint is added as a flavoring agent. Marketed in bottles of 180, 240, 360 and 480 cc.

**Creamalin (Unflavored):** Contains 5.5 per cent aluminum hydroxide (equivalent to 3.6 per cent aluminum oxide). Marketed in bottles of 180 cc. and 480 cc.

**ALUMINUM PHOSPHATE GEL-U. S. P.—Phosphaljel-Wyeth.**—"A water suspension containing not less than 3.8 per cent nor more than 4.2 per cent of  $\text{AlPO}_4$  [aluminum phosphate]."—U. S. P. Flavoring, sweetening and preservatives may be added.

For description and standards see U. S. Pharmacopeia under Aluminum Phosphate Gel.

**Actions and Uses.**—Aluminum phosphate gel has antacid, astringent and demulcent properties analogous to those of aluminum hydroxide gel but will not interfere with phosphate absorption. Because the acid combining power of aluminum phosphate gel is less than one half that of aluminum hydroxide gel of the same concentration, it is necessary to prescribe it in amounts more than twice as great. Indications for the selection of aluminum phosphate gel would include cases of ulcer in which a high phosphate diet could not be continuously maintained or which were accompanied by a relative or absolute deficiency of pancreatic juice or by diarrhea. The available evidence indicates that aluminum phosphate gel gives as good results as aluminum hydroxide gel in the treatment of peptic ulcer when it is employed in sufficient amounts.

**Dosage.**—Fifteen to 30 cc. alone or with water or milk may be administered every two hours during the active stage of the ulcer. Later the dose may be reduced to 45 cc. four times daily (with or after each meal and at bedtime) or to 30 cc. six times daily (with or after and between meals and at bedtime).

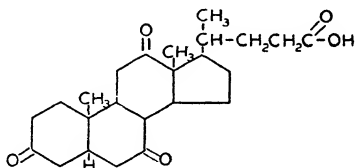
WYETH, INCORPORATED

**Phosphaljel:** 480 cc. bottle. Aluminum phosphate gel containing 4 per cent of aluminum phosphate, 5 per cent of glycerin, not more than 0.5 per cent of sodium benzoate as a preservative and oil of peppermint as a flavoring agent.

U. S. patent 2,294,889. U. S. trademark 397,011.

## CHOLERETICS

**DEHYDROCHOLIC ACID.**—**Decholin-Ames.**—An oxidation product of cholic acid derived from natural bile acids. Its structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Dehydrocholic acid is useful for its ability to increase the volume of the bile (hydrocholeretic action); it does not stimulate evacuation of the gallbladder (it is not a cholagogue); its effect on the secretion of bile constituents (choleretic action) is uncertain. The production of hydrocholeresis may be of value to encourage drainage of the bile ducts by removal of mucus, inspissated bile and debris and to discourage the ascent of infection in these structures in cholecystitis, noncalculous cholangitis and other conditions involving biliary stasis not due to complete mechanical obstruction. It should be kept in mind that a copious flow of bile can accomplish a flushing of the ducts but not, per se, of the gallbladder: the use of dehydrocholic acid in cholecystitis, with or without cholelithiasis, would not therefore be rational in cases where the gallbladder does not fill, except in the presence of stasis of the biliary ducts. In the presence of a decreased output of bile, where the gallbladder fills, hydrocholeresis may indirectly encourage drainage of this viscus if this is induced by the concomitant use of cholagogues. Flushing of the ducts appears less certain in the unoperated patient but may be encouraged by hydrocholeresis in conjunction with an antispasmodic in the presence of spasm of the sphincter of Oddi (spasm of this structure is less readily produced if the liver is secreting freely). Dehydrocholic acid may be employed similarly to encourage maintenance of T-tube surgical drainage of an infected common duct and as an aid in the removal of small stones or foreign material overlooked at operation. It is proposed for the purpose of outlining the bile ducts at operation and of accelerating the appearance of the gallbladder shadow and hastening removal of residual tetraiodophenolphthalein from the biliary tract in cholecystography.

Experimental evidence indicates that dehydrocholic acid does not significantly affect the rate of clearance of jaundice following relief of biliary obstruction and confirms the pharmacologic observation that bile salts do not affect the excretion of bile pig-

ments. A few clinical studies favor the use of the drug in the treatment of arsenical and other forms of toxic hepatitis and of hepatic dysfunction, and as a diuretic—alone or in combination with the mercurials—in the treatment of ascites due to hepatic congestion in cardiac decompensation, cirrhosis or some other form of liver damage, but these have been too poorly controlled to warrant further recognition of such uses until more unequivocal evidence is available.

Dehydrocholic acid acts as a mild diuretic. It has been shown to produce diuresis in edematous patients when this edema is of cardiac origin, but it is less effective than the mercurials for this purpose. However, as is the case with certain other mild diuretics, when given with the mercurials it potentiates their diuretic effect.

Dehydrocholic acid is contraindicated in complete mechanical biliary obstruction because the production of hydrocholeresis in this condition is irrational if not actually harmful. Its use in the presence of severe hepatitis may also be questioned on the ground that this condition may be aggravated or may reduce the hydrocholeric effect, although more evidence is needed on these points before hepatitis can be regarded as a contraindication to the use of the drug.

*Dosage.*—From 0.25 to 0.5 Gm. two to three times daily after meals for a period of four to six weeks.

AMES COMPANY, INC.

**Decholin (Powder):** Bulk. Dehydrocholic acid.

**Tablets Decholin:** 0.243 Gm.

U. S. trademark 315,067.

GEORGE A. BREON & COMPANY, INC.

**Tablets Dehydrocholic Acid:** 0.25 Gm.

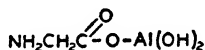
THE HARROWER LABORATORY, INC.

**Tablets Dehydrocholic Acid:** 0.243 Gm.

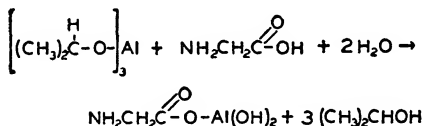
E. S. MILLER LABORATORIES, INC.

**Tablets Dehydrocholic Acid:** 0.243 Gm.

**DIHYDROXY ALUMINUM AMINOACETATE.**—**Al-glyn-Brayten.**—A basic aluminum salt of glycine containing small amounts of aluminum hydroxide and glycine.—The structural formula for basic aluminum aminoacetate may be represented as follows:



Dihydroxy aluminum aminoacetate is prepared by the reaction of aluminum isopropoxide with glycine according to the following reaction:



The precipitated dihydroxy aluminum aminoacetate is filtered with suction, washed with isopropyl alcohol and dried at a temperature not exceeding 71° C. The aluminum isopropoxide is prepared by the reaction of aluminum in shreds or strips with anhydrous isopropyl alcohol, catalyzed by 0.03 per cent mercuric chloride, followed by distillation under vacuum.

For tests and standards, see Section B.

*Actions and Uses.*—Dihydroxy aluminum aminoacetate acts as a gastric antacid when taken orally and is thus useful for the control of hyperacidity in the management of peptic ulcer. It shares the properties of the aluminum hydroxide gel preparations over which it has no important advantages. Its buffer action is not significantly more prompt, greater or more prolonged than that of the liquid preparations of aluminum hydroxide gel when compared on the basis of equivalent aluminum content. Compared with dried aluminum hydroxide gel (U. S. P.) it possesses only slightly more prompt buffering action and shares with that preparation the convenience of tablet form in which it is used. Because it contains from 50 to 60 per cent less aluminum than the aluminum hydroxide preparations, the formation of astringent aluminum chloride in the intestine is theoretically reduced. This is claimed to result in less constipating action. The clinical significance of its slightly more prompt buffering action than dried aluminum hydroxide gel or its tendency to produce less constipation than aluminum hydroxide preparations in general is open to question. Claims that dihydroxy aluminum aminoacetate is generally superior to aluminum hydroxide preparations are disallowed until more clinical evidence is available to demonstrate significant differences. The claimed prompt disintegration in the stomach of dihydroxy aluminum aminoacetate tablets when swallowed whole appears to offer only limited advantage for the ambulant treatment of individuals unable to chew tablet preparations of dried aluminum hydroxide gel since the latter may be readily broken up prior to administration when that becomes necessary.

*Dosage.*—Dihydroxy aluminum aminoacetate is administered orally in tablet form. One to two 0.5 Gm. tablets after meals and at bedtime or as otherwise required to control hyperacidity are recommended. As with other internally administered aluminum compounds, constipation may occur from prolonged administration.

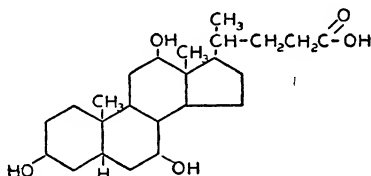
BRAYTEN PHARMACEUTICAL CO.

**Alglyn (Powder):** Bulk.

**Tablets Alglyn:** 0.5 Gm.

U. S. trademark 420,509.

**OX BILE EXTRACT—U. S. P.—Bilein—Abbott.—Glycotauro—H. W. & D.—Bile Salts.**—"Contains an amount of the sodium salts of ox bile acids equivalent to not less than 45 per cent of cholic acid ( $C_{24}H_{40}O_5$ )."  
*U. S. P.* The structural formula of cholic acid may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Ox Bile Extract.

The bile of man and of several animals contains the sodium salts of several conjugated oxycholanic acids in varying proportions. In ox and human biles glycocholic acid and taurocholic acid are prominent constituents. Fresh ox bile is said to contain about 3 per cent each of sodium glycocholate and sodium taurocholate.

**Actions and Uses.**—The bile salts constitute the main active principles of bile, and therefore share the actions and uses of the latter, perhaps with the advantage of more constant composition. When injected into the circulation, they cause severe nervous and cardiac depression, not observed when they are given by the mouth. They are generally credited with a slight antiseptic and laxative action, with enhancing the efficiency of the resinous hydragogue cathartics, and a prominent role in the digestion and absorption of fat. They stimulate the secretory activity of the liver, increasing both the fluids and solids of the bile.

They have been used with doubtful rationale in obstructive jaundice; their use is more reasonable in nutritional disturbances accompanying biliary fistula. There is evidence to indicate that bile salts are useful to promote the intestinal absorption of food fats and fat soluble vitamins when failure to absorb these substances is due to lack of bile in the intestine.

**Dosage.**—From 0.2 Gm. to 0.4 Gm. with water; preferably after meals.

**Preparation.**—Ox bile-extract is made either by dissolving ox bile in alcohol, clarifying and decolorizing the alcoholic solution, followed by evaporation of the solvent (Bilein); or by evaporating the bile and extracting the crude residue with methyl alcohol, filtering the solution and evaporating the solvent (Glycotauro).

## ABBOTT LABORATORIES

**Bilein.**—Dried and purified ox bile. A powdered preparation of ox bile containing not less than 70 per cent of total bile acids, essentially in the form of sodium glycocholate and sodium taurocholate, in the proportion existing in ox bile.

**Capsules Bilein:** 0.3 Gm. Each capsule contains sodium chloride 30 mg. as an excipient.

**Tablets Bilein:** 0.2 Gm. Each tablet contains 12 mg. each powdered magnesium oxide, U. S. P. and talc as excipients.

**Enterabs Bilein:** 0.2 Gm. Each tablet contains 12 mg. each of powdered magnesium oxide, U. S. P. and talc as excipients and is enterically coated.

U. S. Trademark 44,140.

**Capsules Bile Salts:** 0.2 Gm.

## HYNSON, WESTCOTT &amp; DUNNING, INC.

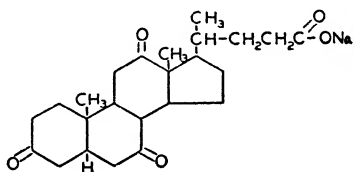
**Capsules Glycotauro:** 85 mg. Concentrated ox bile, freed from bile pigments, containing more than 50 per cent of the natural mixture of sodium glycocholate and sodium taurocholate. Each gram represents approximately 15 cc. of fresh ox bile.

**Enteric Coated Tablets Glycotauro:** 78 mg., enteric coated with salol.

## WINTHROP-STEARNS, INC.

**Bile Salts:** Bulk. A preparation obtained from fresh ox bile, consisting essentially of sodium glycocholate and sodium taurocholate, in the proportion existing in ox bile.

**SODIUM DEHYDROCHOLATE.**—**Decholin Sodium.**—**Ames Company, Inc.**—The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses of sodium dehydrocholate are the same as those of dehydrocholic acid.

After intravenous injection decholin sodium is a mild diuretic. It has been shown to produce diuresis in edematous patients when this edema is of cardiac origin, but it is less effective than

the mercurials for this purpose. However, as is the case with certain other mild diuretics, when given with the mercurials it potentiates their diuretic effect.

Sodium dehydrocholate is also useful in the determination of the arm to tongue circulation time as a diagnostic aid in certain conditions affecting the velocity of the blood flow.

Sodium dehydrocholate is contraindicated in the presence of bronchial asthma.

*Dosage.*—Sodium dehydrocholate is administered intravenously. One injection is given on each of three successive days. According to the urgency of the case, the first dose consists of from 5 to 10 cc. of the 20 per cent solution; the second and third, of 10 cc.

For determination of the arm to tongue circulation time, 3 to 5 cc. are rapidly injected (2 to 3 seconds) through an 18 gauge needle into a cubital vein with the subject in the supine position. The time is recorded from the beginning of injection to the perception of a bitter taste (average normal range 9 to 16 seconds).

AMES COMPANY, INC.

**Solution Decholin-Sodium, 20%:** 3 cc., 5 cc., and 10 cc. ampuls.

U. S. trademark 315,083.

GEORGE A. BREON & COMPANY, INC.

**Solution Sodium Dehydrocholate 20%:** 5 cc. ampuls.

CARROLL DUNHAM SMITH PHARMACAL CO.

**Solution Sodium Dehydrocholate 20%:** 5 cc. vials.

ENDO PRODUCTS, INC.

**Solution Sodium Dehydrocholate 20%:** 3 cc. and 10 cc. ampuls.

### Emollients

**GASTRIC MUCIN.**—The fraction precipitated by approximately 60 per cent alcohol from the supernatant liquid after pepsin-hydrochloric acid digestion of hog stomach linings.

For tests and standards, see Section B.

*Actions and Uses.*—Gastric mucin is prepared for use in the treatment of peptic ulcers.

*Dosage.*—Average dose 2.5 Gm., which can be given at two hour intervals.

Gastric mucin is manufactured by license from the Gastric Mucin Committee of Northwestern University Medical School under U. S. patent 1,829,270 (Oct. 27, 1931; expires 1948).

THE ARMOUR LABORATORIES

**Gastric Mucin (Granules):** 226.8 Gm. and 453.6 Gm. packages.

**Gastric Mucin (Powder):** 226.8 Gm. and 453.6 Gm. packages.

WILSON LABORATORIES

**Gastric Mucin (Granules):** 226.8 Gm. and 453.6 Gm. packages.

**Gastric Mucin (Powder):** 453.6 Gm. packages.

WINTHROP-STEARNES, INC.

**Gastric Mucin (Granules):** 5 Gm. packages and 226.8 Gm. packages.

**Gastric Mucin (Powder):** 226.8 Gm. and 453.6 Gm. packages.

**BISMUTH MAGMA-N. F.—Cremo-Bismuth-Sharp & Dohme.—Lac-Bismo-Hart.**—"Bismuth Magma contains bismuth hydroxide and bismuth subcarbonate in suspension in water and yields not less than 5.2 per cent and not more than 5.8 per cent of  $\text{Bi}_2\text{O}_3$ ."—N. F.

For description and standards see The National Formulary under Bismuth Magma.

*Actions and Uses.*—Used in digestive disturbances.

*Dosage.*—From 4 to 15 cc. every two or three hours.

E. J. HART & COMPANY, LTD.

**Lac Bismo:**

U. S. trademark 52,250.

SHARP & DOHME, INC.

**Cremo-Bismuth:**

U. S. trademark 29,335.

## Laxatives

**AGAR-U. S. P.—Agar-Agar.**—"The dried hydrophillic colloidal substance extracted from *Gelidium cartilagineum* (Linné) Gallion (Fam. *Gelidiaceae*) and from related red algae (Class *Rhodophyceae*)." U. S. P.

For description and standards see the U. S. Pharmacopeia under agar.

*Actions and Uses.*—Passes through the intestinal canal almost unchanged. Absorbs and retains moisture, and acts as an intestinal demulcent and lubricant. Used in chronic constipation of intestinal atony; renders the feces soft and bulky and thus promotes peristalsis.

*Dosage.*—4 Gm.

MERCK & CO., INC.

**Agar-Agar (Flakes and Powder):** Bulk.



**LIQUID PETROLATUM-U. S. P.—Petrogalar-Wyeth.**  
—Liquid Paraffin.—White Mineral Oil.—Heavy Liquid Petrolatum.—“A mixture of liquid hydrocarbons obtained from petroleum.” *U. S. P.*

For description and standards see the *U. S. Pharmacopeia* under Liquid Petrolatum and Liquid Petrolatum, Emulsion and the *National Formulary* under Petrolatum, Liquid, Emulsion with Phenolphthalein.

*Actions, Uses and Dosage.*—Liquid petrolatum is used in the treatment of constipation to keep the stools soft. Practically none is absorbed by the intestine and it has no nutritive properties. When present in the upper part of the intestinal tract, it may interfere with the absorption of carotene (but not with the absorption of Vitamin A itself), so that liquid petrolatum should not be taken before nor shortly after meals. 15 cc. doses should be administered at bedtime or in the morning before eating; if necessary, it may be given one or two hours before lunch or dinner.

THE E. L. PATCH COMPANY

**Emulsion Kondremul (Plain):** 500 cc. bottles. An emulsion of mineral oil and Irish Moss (*Chondrus Crispus*).

**Emulsion Kondremul with Cascara:** 400 cc. bottles. An emulsion of mineral oil with non-bitter extract of cascara and Irish Moss (*Chondrus Crispus*).

**Emulsion Kondremul with Phenolphthalein:** 500 cc. bottles. An emulsion of mineral oil with phenolphthalein and Irish Moss (*Chondrus Crispus*).

SMITH-DORSEY COMPANY

**Emulsion Liquid Petrolatum (Chocolate Flavored):** A palatable emulsion containing 60 per cent (by volume) of liquid petrolatum, 1 per cent agar-agar per 30 cc. and 0.1 per cent of benzoic acid.

**Emulsion Liquid Petrolatum with 0.1 Gm. Phenolphthalein (Chocolate Flavored).**

**Emulsion Liquid Petrolatum with 0.3 Gm. Phenolphthalein (Chocolate Flavored).**

SMITH OIL & REFINING COMPANY

**Mineral Oil:** Bulk.

E. R. SQUIBB & SONS

**Mineral Oil:** 180 cc., 480 cc. and 960 cc. bottles.

**Emulsion Mineral Oil:** Mineral oil, 50 cc.; sodium alginate, 0.49 Gm.; methyl cellulose, 0.25 Gm.; sodium benzoate, 0.10 Gm.; glycerin, water and flavoring sufficient to make 100 cc.

**Emulsion Mineral Oil and Phenolphthalein:** Mineral oil emulsion with 0.33 Gm. phenolphthalein per 100 cc.

WYETH, INC.

**Emulsion Petrogalar:** Liquid petrolatum 65% emulsified with 0.5% sodium alginate in a menstruum containing glycerin, agar, aracia, saccharin, flavoring, benzoic acid and water to make 100 cc. Contains phthalein 0.32 Gm. Contains sodium benzoate 0.065 per cent as preservative.

**Emulsion Petrogalar Alkaline:** Petrogalar with magnesia oxide 0.48 per cent per 100 cc., glycerin 6.7 per cent. No saccharin or preservative.

**Emulsion Petrogalar with Cascara:** Petrogalar with non-bitter fluid extract of cascara sagrada 7.4 per cent per 100 cc., karaya 0.15%, glycerin 0.5%, flavoring, saccharin 0.03% and sodium benzoate 0.07 per cent as preservative.

**Emulsion Petrogalar with Phenolphthalein:** Petrogalar with phenolphthalein 0.32 per cent. Contains sodium benzoate 0.065 per cent as preservative.

**Emulsion Petrogalar Unsweetened:** Petrogalar with saccharin omitted. Contains sodium benzoate 0.06 per cent as preservative.

U. S. trademark 165,616.

**PETROLATUM-U. S. P.**—Petroleum Jelly.—“A purified, semi-solid mixture of hydrocarbons obtained from petroleum.”  
*U. S. P.*

For description and standards see the U. S. Pharmacopeia under Petrolatum.

*Actions, Uses and Dosage.*—Petrolatum is used chiefly as an ointment base. Sterilized petrolatum is employed as a lubricant.

SARGENT'S DRUG STORE

**Petrobran:** Each 100 Gm. contains: petrolatum, 74 Gm.; bran, 22 Gm.; with powdered licorice and “oil of pineapple” (ethyl butyrate) sufficient to flavor.

**PSYLLIUM HYDROPHYLIC MUCILLOID WITH DEXTROSE.**—Metamucil-Searle.—A mixture containing about 50 per cent of powdered mucilaginous portion (outer epidermis) of blonde psyllium seeds (*Plantago ovata*-Forsk) and powdered anhydrous dextrose, with sodium bicarbonate 0.2 per cent, monobasic potassium phosphate 0.25 per cent, citric acid 0.33 per cent and benzyl benzoate 0.04 per cent.

For tests and standards, see Section B.

*Actions and Uses*—Psyllium hydrophylic mucilloid with dextrose is intended as an adjunct in the treatment of constipation. It encourages elimination by the formation of a soft, plastic,

water-retaining gelatinous residue in the lower bowel. The mucilloid is also claimed to have a demulcent effect in the presence of inflamed mucosa. Psyllium hydrophylic mucilloid with dextrose has been mixed with barium sulfate to obtain more uniform dispersion of the barium for x-ray visualization.

*Dosage.*—Four to 7 Gm. one to three times daily, each dose thoroughly stirred in a glass of water and followed by an additional glass of liquid. Children receive proportionate amounts according to weight and age. It is important that adequate fluids be ingested to assure a soft bulk. Psyllium hydrophylic mucilloid with dextrose should not be used carelessly so that a state of dependency is reached.

G. D. SEARLE & Co.

**Metamucil:** 113 Gm., 227 Gm. and 454 Gm. containers.

U. S. patent 2,095,259 (Oct. 12, 1937; expires 1954). U. S. patent 2,132,484 (Oct. 11, 1938; expires 1955), U. S. trademark 317,704 (Oct. 2, 1934).

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## CHAPTER XVI

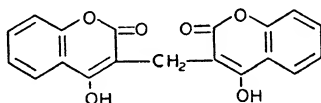
# Hematics

This chapter includes agents that exert an effect on the blood itself. It thus comprises principally (1) agents that influence the production of formed elements and (2) agents that affect the coagulation of the blood.

The former group includes iron compounds and certain preparations from liver and stomach; these are used to increase the rate of production of normal red corpuscles by the bone marrow. The group of substances affecting coagulability may be subdivided into those having a general and those having a local effect. The local effect is illustrated by various coagulation-accelerating products (e.g. thromboplastic brain extracts, thrombin, fibrin foam, and oxidized gauze), which promote coagulation when applied directly to bleeding surfaces; some such preparations are described in this chapter. The general effect is illustrated by the systemic administration of heparin, which delays coagulation and of vitamin K, which accelerates coagulation under certain circumstances of hypoprothrombinemia. Preparations of vitamin K are described in the chapter on Vitamins and Vitamin Preparations.

## Anticoagulants

**DICUMAROL.**—3,3'-methylenebis(4-hydroxycoumarin).—The structural formula of dicumarol may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Dicumarol causes a lengthening of the prothrombin time by decreasing the prothrombin concentration of the blood. Although the exact mode of action is not known, it is assumed that dicumarol acts on the liver to retard prothrombin production, since the circulating prothrombin present in blood is not affected *in vitro* by the addition of dicumarol; the dicumarol effect requires 12 to 24 hours to develop; and the effect persists for from 24 to 72 hours after discontinuance of therapy.

Dicumarol may be used in the prophylaxis and treatment of

intravascular clottings. It may be used alone or as an adjunct to heparin in the treatment of postoperative thrombophlebitis and pulmonary embolism, acute embolic and thrombotic occlusion of peripheral arteries and recurrent idiopathic thrombophlebitis.

Dicumarol does not affect thrombi or emboli already present nor does it increase the local blood supply of an area affected by an embolus. Dicumarol can only be expected to retard further intravascular clotting and prevent propagation of the thrombus or embolus.

Since the ultimate outcome of acute coronary thrombosis is to a large extent dependent upon extension of the clot and upon the formation of mural thrombi in the heart chambers with subsequent embolization, dicumarol has been used as an adjunct in the treatment of this condition.

*Dosage.*—On the first day the prothrombin time is determined to insure that it is not abnormally high. One dose of 200 to 300 mg. is given, depending on the size and condition of the patient. On the second day the per cent prothrombin is determined, and a second dose of 100 to 200 mg. of dicumarol is given only if the activity is more than 25 per cent. On successive days 100 to 200 mg. is administered if prothrombin activity is more than 25 per cent.

If prothrombin activity drops below 15 per cent, or if signs of bleeding appear, menadione sodium bisulfite, 72 mg. is given intravenously slowly. This may be given along with transfusions of fresh whole blood.

ABBOTT LABORATORIES

**Tablets Dicumarol:** 25 mg., 50 mg. and 0.1 Gm.

THE WM. S. MERRELL COMPANY

**Tablets Dicumarol:** 100 mg.

U. S. trademark 398,198. The Wisconsin Alumni Research Foundation for the anti-coagulant 3,3'-methylenebis(4-hydroxycoumarin).

**HEPARIN SODIUM.**—The hydrated sodium salt of a naturally occurring, complex organic polymer possessing anti-coagulant properties. The chemical structure of heparin has not been fully established. It is considered to be a dextrorotatory polysaccharide made up of hexosamine and hexuronic acid units containing sulfuric acid ester groups. Heparin is found in a large number of body tissues, and is believed to be closely connected in formation with the mast cells of the body. Heparin sodium may be prepared from liver or lung tissue by a modification (Kuizenga and Spaulding: *J. Biol. Chem.* 148: 641, 1943) of the method of Charles and Scott (*Biochem. J.* 30: 1927, 1936). The product is further purified for medicinal use.

Heparin sodium is standardized to possess not less than 100 units of anticoagulant activity per milligram of dry material, by the sheep plasma coagulation method (Kuizenga, Nelson and

Cartland: *Am. J. Physiol.* 139:612, 1943). The standard of potency is the Provisional International Standard, a dried preparation of the sodium salt of heparin to which has been assigned a potency of 130 units per milligram (*League of Nations, Bulletin of the Health Organization*, Vol. X, No. 2, p. 151, 1942-1943). This Provisional International Standard is to be used only as a standard of potency.

For tests and standards, see Section B.

**Actions and Uses.**—Heparin sodium has the property of inhibiting blood coagulation. It may aid the normal body to maintain blood in a fluid state as traces are detectable in the blood. Very little is known concerning the metabolism, excretion and fate of heparin sodium in the body. Its anticoagulant action appears to be effected by action on the thrombin, which with fibrinogen forms fibrin.

The exact status of heparin sodium in surgery and medicine has not been determined, but it is claimed to be of value as a substitute for citrate in blood transfusions, in an attempt to prevent postoperative thrombosis and possibly thrombosis of other origin, the prevention of recurring thrombosis in phlebitis and pulmonary embolism, and other uses. It has been used alone and with sulfonamides in the treatment of subacute bacterial endocarditis, but much work remains to be done before this procedure can be generally accepted; results have not been impressive.

**Dosage.**—The potency of heparin sodium is expressed in units. Ampul solutions keep indefinitely, and may be sterilized by boiling or autoclaving at 110 C. for thirty minutes. The substance is inactive orally and is usually injected intravenously. It may be given by single injection or continuous intravenous drip, the infusion being adjusted by watching the coagulation time. The clotting time should be maintained between fifteen and twenty minutes. If a chill develops or spontaneous bleeding occurs, the drug should be stopped. When the interrupted dose method is employed, 50 mg. (5,000 units) may be administered at intervals of four hours up to a total of 250 mg. per day. For continuous drip, 100 to 200 mg. (10,000 to 20,000 units) is added to 1,000 cc. of 5 per cent sterile dextrose or isotonic sodium chloride solution. The flow may be started at about twenty drops per minute.

#### ABBOTT LABORATORIES

**Solution Heparin Sodium:** 10 cc. vials. Each cubic centimeter contains 1,000 provisional international units (approximately 10 mg.) of heparin sodium, preserved with 0.5 per cent phenol.

#### UPJOHN COMPANY

**Solution Heparin Sodium:** 10 cc. vials. Each cubic centimeter contains 10 mg. of heparin sodium, preserved with 0.5 per cent chlorobutanol.

## Iron and Iron Compounds

Iron is used in medicine: (1) in the form of metallic or elementary iron (reduced iron, U. S. P.); (2) in the ferrous or unoxidized form of combination—responding to tests for ferrous ions (ferrous carbonate in mass of ferrous carbonate and pill of ferrous carbonate, ferrous iodide in syrup of ferrous iodide); (3) in the trivalent or oxidized form, the ferric compounds—responding to tests for ferric ions (ferric chloride in tincture of ferric chloride); and (4) in the form of complex compounds of iron.

Complex (masked or nonionic) iron compounds are those compounds of iron whose solutions do not respond to the ordinary tests for ferrous or ferric ions because in them the iron is part of a radical. Complex compounds of iron do not have the astringent taste of simple iron solutions. The permanence of these complex radicals differs widely; while some, such as soluble ferric phosphate, N. F., and solution of peptonized iron, are converted to simple ionic iron by action of dilute acids, others resist treatment with strong acids or with alkalis. The complex iron compounds occurring naturally in animal and vegetable tissues (which are often termed food irons) belong generally to the more resistant class, while the complex iron compounds produced artificially are as a rule decomposed rather readily. There is, however, no sharp line of distinction between the natural complex iron compounds and those products artificially produced, nor is there any good evidence that they differ in therapeutic action. Until a difference in their effects has been demonstrated, we may class together all complex iron compounds whose solutions are not decomposed into simple ionic iron by digestion at body temperature with 0.2 per cent hydrochloric acid and pepsin. (It should be emphasized that salts of iron which give the iron test directly are classed as inorganic iron, whatever their acid radicals may be, and that true iron albuminate and iron peptonate are inorganic iron compounds.)

*Actions and Uses.*—Solutions of ferric iron are used externally as styptics. Tincture of ferric chloride is an astringent and is used in applications to the throat. The principal use of iron, however, is in the treatment of anemia and chlorosis. For this purpose, the ferrous salts are usually preferred to the ferric salts, as they are not so caustic and hence are less likely to disturb the stomach. Reduced iron, yielding ferrous chloride when dissolved in the stomach, acts as a ferrous compound, provided the hydrochloric acid in the gastric fluid is sufficient to permit solution. So far as the complex iron compounds are not decomposed by gastric digestion, they also are devoid of gastric effects; but, on the other hand, it has been claimed that certain hemoglobin-like compounds escape absorption altogether. Bunge supposed that only "organic iron" could be absorbed and assimilated by the body, the reputed action of inorganic iron being altogether indirect and due to its local effect on the alimentary

canal. This theory was modified by Abderhalden to the effect that inorganic iron, while it could not be converted into hemoglobin, nevertheless stimulated the conversion of "organic iron." Later work (Tartakowski), however, proves that inorganic iron is assimilated and converted into hemoglobin and it is in fact therapeutically more effective than natural complex iron compounds. Whipple and his co-workers have shown that ferrous carbonate (in the form of Bland's Pills) aids recovery from the anemia of repeated hemorrhages. Starkenstein (Heffner-Heubner Handbuch der experimentelle Pharmakologie) reports that Reiman has shown that ferrous salts are effective in bringing about a reticulocyte response, hemoglobin and red blood cell increase in much smaller amounts than the ferric salts; 100 mg. of iron as ferrous salts daily were shown to be effective. A difference exists between the different iron preparations in their local irritant and astringent action, which is absent in most of the complex iron compounds. These local actions may be desirable in some cases and undesirable in others. This should mainly determine the selection of the particular iron preparation most suitable for each patient. Suitable diet (especially liver, kidney, meat and spinach) is sometimes more effective than the iron preparations, presumably by the cooperation of other factors; for in pernicious anemia, liver extract that is practically iron-free is equally active.

### *Simple Iron Salts*

**FERROUS LACTATE.**—Iron Lactate.— $\text{Fe}(\text{C}_3\text{H}_5\text{O}_3)_2 + 3\text{H}_2\text{O}$ .—The ferrous salt of lactic acid. The salt contains approximately 19 per cent of metallic iron.

For tests and standards, see Section B.

*Actions and Uses.*—Ferrous lactate is a mild chalybeate, which, because of its feeble taste, may be taken without difficulty.

*Dosage.*—From 60 mg. to 1.3 Gm. Owing to its liability to oxidation, it is best prescribed in solutions containing much sugar. Syrup dissolves 1 Gm. in 120 Gm.

### *Complex Iron Salts*

**FERRIC AMMONIUM CITRATE.**—U. S. P.—"Contains ferric citrate equivalent to not less than 16.5 per cent and not more than 18.5 per cent of Fe [iron]."—U. S. P.

For description and standards see the U. S. Pharmacopeia under Ferric Ammonium Citrate and Ferric Ammonium Citrate Capsules.

*Actions and Uses.*—See general article, Iron and Iron Compounds. Ferric ammonium citrate is a hematinic which is practically nonastringent.

*Dosage.*—1 Gm.

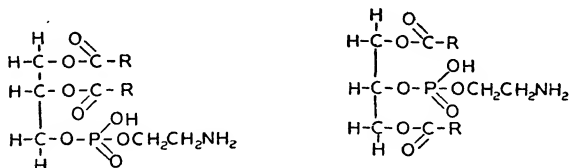


## Fibrin Ferments and Thromboplastic Substances

The clotting of blood (that is, the transformation of the fibrinogen of circulating blood into the insoluble fibrin of blood clot) has been shown to be due to the action of the fibrin ferment (thrombin) on the fibrinogen of the blood. The fibrin ferment of thrombin exists in the blood in the form of its fore-runner (prothrombin) which is acted on by the calcium salts and converted into thrombin. Besides calcium salts, however, another factor is necessary. This other factor may be furnished by the breaking down of blood cells or blood platelets or by injured tissues. It has been designated as "zymoplastic" substance by Schmidt, as "thrombokinase" by Morowitz, and as "thromboplastic substance" or "thromboplastin" by Howell.

**Actions and Uses.**—Preparations containing thromboplastin are said to be useful when applied locally in the treatment of hemorrhage, especially hemorrhage from oozing surfaces, likewise in the treatment of scar tissues, in nosebleed, and in surgery of the bones, glands, nose and throat. Intravenous injection is dangerous, and there is no satisfactory evidence that subcutaneous injection is useful. Preparations should be standardized by testing specimens of blood *in vitro* and should reduce the coagulation time significantly. They should be proved to be sterile. The Council holds that there is no evidence to warrant the internal use of these substances, and further that such use, on account of the danger from anaphylaxis from preparations containing animal proteins, is likely to be harmful unless proper precautions are taken. There appears to be no evidence that this danger is connected with local applications, but even before such use physicians should inquire into the patient's history to determine whether or not sensitivity to these proteins exists.

**BRAIN LIPOID.**—Impure Cephalin.—Impure Kephalin.—An extract of the brain of the ox, or other mammal, prepared according to the method of Howell as applied in practice by Hirschfelder (*Lancet* 2:542, 1915) and described below. The structural formulas of  $\alpha$ - and  $\beta$ -cephalin may be represented, respectively, as follows:



**Actions and Uses.**—See general article, Fibrin Ferments and Thromboplastic Substances.

**Dosage.**—Brain lipid may be spread on gauze sponges, on pledgets, or on the tissues themselves; or an emulsion may be

prepared by shaking up with physiological solution or sodium chloride and used in the same way or sponged over the tissues.

For use in an office or dispensary, a 5 per cent ethereal solution of brain lipid suffices and can be kept ready for use for some time (several months) in a sterile dropper bottle from which an opalescent emulsion can be prepared extemporaneously by dropping from 10 to 30 drops into an ounce of isotonic solution of sodium chloride and then shaking. This solution can also be dispensed by pharmacists, provided the opening in the stopper of the dropper bottle is kept slightly open to prevent the ether's blowing off when the bottle is shaken or heated.

#### *Preparation.*—

Brain lipid (impure cephalin) is prepared from ox brain which is run through a hashing machine, then covered with 3 volumes of alcohol and agitated two or three times. The excess of alcohol is then poured off and squeezed out gently through linen, care being taken to avoid great force in wringing out the alcohol, as this tends to break up the brain tissue into very finely divided particles which pass through the filter. The residue is then covered with 3 volumes of ether, shaken vigorously and filtered first through cotton and then through filter paper. The clear filtrate thus obtained is evaporated to dryness over a water bath, leaving a yellow residue of fatty appearance and consistency. (This residue consists largely of cephalin, but though the latter is not in the pure state, it is extremely active in accelerating the clotting of blood *in vitro*.)

The method of preparation renders it sterile. It can be transferred on a sterile spatula or knife blade to sterile vessels. It retains its activities for several weeks.

(The impurities, largely the lecithins and myelins, do not materially interfere with the activity of the cephalin, but, on the contrary, facilitate its emulsification in isotonic solution of sodium chloride and thus facilitate its intimate miscibility with blood.)

**SOLUTION BRAIN EXTRACT.**—Solution Thromboplastin-Hess.—An extract of cattle brain in isotonic solution of sodium chloride prepared by the method of Hess (*J. A. M. A.* 66: 558 [Feb. 19] 1916, footnote 2).

*Actions and Uses.*—See general article, Fibrin Ferments and Thromboplastic Substances.

*Dosage.*—The solution may be applied directly to the bleeding tissues or sprayed on them, or a sponge or tampon may be immersed in it and then pressed on the bleeding surface.

#### *Preparation.*—

Cattle brains are obtained fresh from the slaughter-house, stripped of their membranes, washed in running water and weighed. They are then passed through a meat chopping machine three times, and to the quantity prepared an equal quantity of isotonic solution of sodium chloride is added. This suspension is allowed to remain in the refrigerator for forty-eight hours, and is then pressed through cheese-cloth twice. This extract, which contains fine suspension of tissue in addition to tissue juice, is diluted with one half its volume of physiological solution of sodium chloride. Cresol is then added in proper proportion so that the finished preparation contains 0.3 per cent. It maintains its hemostatic potency for some time (several months). (As cresol is not a perfect antiseptic, the sterility of this preparation cannot be guaranteed.)

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Thromboplastin Local:** 20 cc. vials.

*Clinical Assay.*—

The potency of Thromboplastin Local-Lederle is tested as follows: Transfer 0.5 cc. of oxalated blood plasma (0.1 per cent oxalate) to each of a series of tubes, and add 0.2 cc. of Thromboplastin Local-Lederle to each tube. Also transfer 0.5 cc. of oxalated blood plasma to each of a control series of tubes and add 0.2 cc. of physiologic solution of sodium chloride. To each tube (and control) add 0.2 cc. of calcium chloride solution the strength of which is determined by control tests as follows: that dilution of calcium chloride (usually 0.15, 0.25 or 0.5 per cent) is chosen with which the plasma forms solid clots in not less than 20 minutes: Thromboplastin Local-Lederle must cause clotting of the oxalated blood (such as to permit complete inversion of the tubes) within one and one-half minutes; the controls must fail to show clotting at the expiration of 20 to 30 minutes.

**THROMBIN, TOPICAL.**—Thrombin.—A preparation of thrombin isolated from bovine or human plasma. It complies with the requirements of the National Institute of Health of the United States Public Health Service.

For tests and standards, see Section B.

*Actions and Uses.*—Thrombin is intended as a hemostatic for topical application to control capillary bleeding in operative procedures. It may be applied as a dry powder or dissolved in sterile, isotonic saline solution. *It should never be injected.*

*Dosage.*—As a dry powder or in solutions containing 1,000 to 2,000 thrombin units.

PARKE, DAVIS & Co.

**Thrombin Topical (Bovine Origin):** 5,000 units. Each ampul contains 5,000 units of thrombin, packaged with a 5 cc. vial of sterile isotonic saline solution preserved with phemerol 1:50,000.

## Liver and Stomach Preparations

Whole liver, extracts of liver and dried stomach stimulate maturation of erythrocytes in pernicious anemia and in certain other macrocytic anemias. The Council has accepted only those preparations of liver or stomach which are primarily intended for the treatment of pernicious anemia.

The daily ingestion of 200 to 400 grams of whole liver is effective in inducing a remission in pernicious anemia and in maintaining a normal red blood cell count. Concentrates for oral administration are made from such amounts of liver, but these have lost a certain amount of the original activity of the liver from which they are derived. Extracts suitable for parenteral administration may be prepared from 10 to 15 Gm. of liver and these possess a therapeutic potency equal to that of the larger amounts of liver given by mouth. Similar effects can be produced by 30 to 40 Gm. of desiccated stomach and by combinations of stomach tissue and liver.

For liver extracts and for preparations of stomach the minimum dose is 1 U. S. P. unit per day, or in the case of intramuscular liver preparations multiples of this at longer intervals (e.g. 7 units per week). A U. S. P. unit is the minimum amount which, when given daily to a suitable patient with pernicious anemia in relapse, will cause an adequate hematopoietic response. Inasmuch as material derived from about thirty times as much liver must be given by mouth to produce the same response as when given by injection, it has been necessary to define the "unit" either as an "oral" unit or as an "injectable" unit according to the method of administration of each preparation. For the purpose of standardization (not as a plan to be followed routinely in the treatment of patients) the material is given daily with proper hematopoietic checks to at least three patients whose red blood cell counts are determined before treatment is started, on the day that it is started, and on the seventh day and the fourteenth day of treatment. Daily reticulocyte counts are made during the complete period of the "reticulocyte response." These data are submitted by the manufacturer to the Anti-Anemia Preparations Advisory Board of the United States Pharmacopeia which evaluates them and assigns unitage. The board has ruled that at present a strength greater than 15 units per cubic centimeter will not be assigned to a preparation because of the possibility of loss, during the concentration process, of unknown factors of value in the treatment of patients with pernicious anemia.

In assigning units to preparations of liver extract or other anti-anemia preparations, the following points are considered by the board in connection with other available data from therapeutic tests conducted in the manner specified.

1. The character and degree of the reticulocyte response.
2. Rate of increase of red blood cells.
3. Clinical factors modifying these responses.
4. Efficiency of the method of manufacture in preserving the potency of the product.
5. The following figures are especially useful to the board in assigning unitage.

Initial Red Blood Cell Count (Millions per Cubic Millimeter)	Peak of Reticulocyte Curve (per Cent)
1.0	41
1.5	28
2.0	18
2.5	11
3.0	5

These figures are not to be considered as "standards," inasmuch as modifying factors, in each individual patient, may change the interpretation of the type and degree of the response. Under some circumstances a higher or lower response would be expected, making the figures in the table inadequate to express the "normal" for every patient. The ideal test patient should

have a red blood cell count between 1 and 2.5 million per cubic millimeter, and should not have received anti-anemic medication or blood transfusion during the previous month. Infection, marked neurological involvement, extensive arteriosclerosis, severe diarrhea, vomiting or marked gastrointestinal complications are factors which must be taken into account in evaluating the response.

The Council requires that all submitted preparations designed for use in the treatment of pernicious anemia be manufactured by a satisfactory method and that they be labeled with a statement of the number of cubic centimeters or grams of material which constitute an "oral" or "injectable" unit as the case may be. The labeling must also conform to the requirements of the Food & Drug Administration.

**FOLIC ACID** (See under Folic Acid Preparations).

**LIVER-STOMACH CONCENTRATE.**—**Extralin-Lilly.**—Liver with Stomach is a brownish powder resulting from mixing a concentrated water solution of mammalian liver with minced fresh hog stomach tissue. The fraction of liver employed contains that portion which is soluble in approximately 70 per cent alcohol by volume and insoluble in approximately 95 per cent alcohol by volume. After admixture and incubation, the product is dried under reduced pressure and defatted. The daily oral administration of 6 Gm. has been found to produce the standard reticulocyte response defined as 1 U. S. P. unit (oral) when assayed in cases of pernicious anemia as required by the Council.

*Actions and Uses.*—Extralin is proposed for use in the oral treatment of pernicious anemia. See general article, Liver and Stomach Preparations.

*Dosage.*—For cases of pernicious anemia in relapse, an initial dosage of 2 Gm. (four pulvules) three times daily is suggested; 1.5 Gm. (three pulvules) three times daily constitutes an adequate maintenance dose for most cases. The amount necessary for maintenance varies with different individuals and can be determined only after repeated examinations.

*Preparation.*—

An extract containing the Cohn fraction D is prepared by grinding mammalian livers into water, adjusting the mixture to the iso-electric point (approximately pH 5 to pH 6), and heating to about 80 C. to coagulate protein; this is stirred for thirty minutes and filtered; the filtrate is reduced under vacuum to small volume. This extract is then admixed with finely minced fresh hog stomachs or fresh hog stomach linings. The hydrogen ion concentration is adjusted to approximately pH 5 and the mixture allowed to interact or digest for about two hours at 37.5 C. It is then spread out in a thin layer on pans and dried under vacuum. The dried product is removed from the drier and ground, then extracted with petroleum ether to remove fat. This is dried under vacuum and ground to the proper fineness. The proportions used are such that there is represented in the finished product two to four parts of original liver to one part of original stomach tissue material.

ELI LILLY AND COMPANY

**Pulvules Extralin:** 0.5 Gm. Twelve pulvules supply the equivalent of 1 U. S. P. oral unit of liver.

U. S. patent 1,894,247 (Jan. 10, 1933; expires 1950). U. S. trademark 290,233.

**POWDERED STOMACH-U. S. P.**—Dried Stomach.—“The dried and powdered defatted wall of the stomach of the hog, *Sus scrofa* Linné var. *domesticus* Gray (Fam. *Suidae*). It contains factors which cause an increase in the number of red blood corpuscles in the blood of persons suffering from pernicious anemia. The activity is readily destroyed when the preparation is suspended in hot liquid. The approximate anti-anemic potency of Powdered Stomach in pernicious anemia is expressed in U. S. P. Units (oral). Powdered Stomach conforms to all other provisions outlined under *Anti-anemia Preparations*.”—U. S. P.

For descriptions and standards see U. S. Pharmacopeia under Stomach, Powdered.

*Actions and Uses.*—Dried stomach is used in the treatment of pernicious anemia. See general article, Liver and Stomach Preparations.

*Dosage.*—The average daily dose should not be less than the amount required to furnish 1 U. S. P. oral unit. Larger doses may be necessary in relapse and in severe or complicated cases. The required doses may be administered in a half glassful of water, milk or fruit juice.

PARKE, DAVIS & COMPANY

**Ventriculin:** 100 Gm. and 500 Gm. bottles. Dried stomach 40 grams of material prepared by the method employed in producing the contents of this bottle constitutes 1 U. S. P. unit (oral).

U. S. patent 1,937,133. U. S. trademark 270,811.

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## CHAPTER XVII

# Hormones and Synthetic Substitutes

This chapter includes substances that are internally secreted by particular organs whence they are carried by blood or lymph to other organs for the control of growth or activity. Such substances are called endocrine secretions or hormones. Included here also are a number of artificial substances that are important in therapeutics because their actions so closely resemble those of the natural substances. Epinephrine is described in the chapter on Autonomic Drugs.

### Adrenals

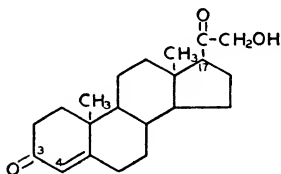
#### *Adrenal Cortex*

The cortex of the adrenal gland is essential for life. Adrenalectomized animals die in a few days. During the acute stages of adrenal insufficiency, occurring in disease or as the result of experimental procedures in animals, conditions commonly observed include blood concentration, low blood pressure, gastrointestinal disturbances, asthenia, subnormal temperature and low basal metabolic rate. There also may be found loss of sodium and retention of potassium in most species, loss of carbohydrate reserves with hypoglycemia and retention of nitrogenous products in the blood. Injections of suitable extracts of adrenal cortex which contain little or no epinephrine may restore even moribund animals to apparently vigorous health for as long as the injections are continued, especially if sodium chloride and water are administered concurrently.

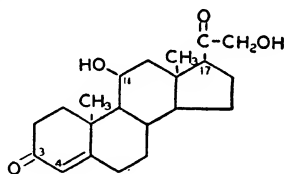
Extracts of the adrenal cortex contain several potent substances which influence to a variable degree electrolyte, water or carbohydrate metabolism; however, as demonstrated on small animals, no one of these substances and no synthetic substance seems to possess all of the effects of a potent cortical extract.

Crystalline compounds have been isolated from the cortex which are capable of maintaining the life of adrenalectomized animals and restoring toward normal the metabolic conditions induced by adrenal insufficiency. These compounds are steroids. The most potent of them are those whose structural formulas are shown below, i.e., desoxycorticosterone (A), corticosterone (B), dehydrocorticosterone (C) and 11-dehydro-17-hydroxycorticosterone (D). Many other steroids have been isolated from this tissue, but most of these have little known physiologic activity.

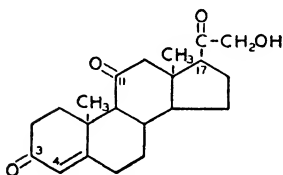
The chemical structure of the cortical steroids is closely related to that of the sex hormones; in fact, some of the cortical steroids have estrogenic or androgenic properties and, in certain



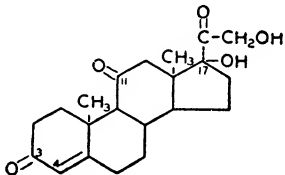
(A)



(B)



(C)



(D)

abnormal conditions of the cortex, large amounts of estrogens or androgens may be recovered in the urine. On the other hand, the sex hormone progesterone has life maintaining properties in adrenal insufficiency in small animals, while other sex hormones such as estrone and testosterone are capable of inducing slight electrolyte changes similar to those produced by cortical steroids.

Adrenal cortex extracts have been assayed in many ways. There are advantages to each of the various methods, but it appears that the maintenance of life in the adrenalectomized animal is the most significant measure of activity for such extracts. For purposes of N. N. R. description, the Council has recognized the assay method devised by Pfiffner, Swingle and Vars (*J. Biol. Chem.* 104:701, 1934) or the slight modification used by Cartland and Kuizenga (*Am. J. Physiol.* 117:678, 1936). By these methods the activity of adrenal cortex preparations is expressed in terms of dog units for uniformity of labeled potency. An alternate assay method using adrenalectomized rats according to the procedure of Cartland and Kuizenga (*Am. J. Physiol.* 117:678, 1936) may also be employed and the results transposed in terms of dog units, provided sufficient data are presented that such a comparison of assays is justified. No preparation of adrenal cortex extract will be accepted for inclusion in New and Nonofficial Remedies that does not have a minimum of 50 dog units or 2.5 rat units per 1.0 cc. of extract when assayed by the Cartland and Kuizenga method.

Desoxycorticosterone, one of the components of adrenal cortex but which is prepared synthetically, is capable of maintaining life



in adrenalectomized animals. Desoxycorticosterone differs from extracts of the adrenal cortex in being even more inactive by mouth and in being chiefly concerned with salt and water metabolism. The adrenal cortex has other activities such as a role in the regulation of carbohydrate, fat and protein metabolism. Therapy with desoxycorticosterone is promising but obviously does not restore full adrenal cortical function. The status of this therapy, including the possibility of harmful reactions and contraindications, is discussed in a Council report (*J. A. M. A.* 114: 2549, 1940).

**ADRENAL CORTEX EXTRACT.**—An extract of adrenal glands, from domesticated animals used as food in man, containing the cortical steroids essential for the maintenance of life in adrenalectomized animals. Only traces of epinephrine are present.

*Actions and Uses.*—Although the extract is active by mouth, this method of administration for therapeutic purposes is not to be depended upon. The usual methods of administration are subcutaneous, intramuscular or intravenous injection. The extract is of value in the treatment of Addison's disease or of adrenal insufficiency of other types, and in surgical procedures involving the adrenal cortex when prophylactic measures are needed to prevent the development of temporary adrenal insufficiency. There is as yet no conclusive proof of the value of the extract in the so-called borderline cases of adrenal insufficiency.

*Dosage.*—The amount required for therapeutic purposes varies widely according to the degree of cortical insufficiency, the condition of the patient, the presence of infection or other complications, and during a crisis. The clinical response of the patient should govern the dosage. As much as 2,500 to 5,000 dog units within a few hours may be required for a patient in a severe crisis, while from 500 dog units daily may be sufficient substitution in many cases of Addison's disease. Large amounts of sodium chloride or other sodium salts are of definite value in supplementing adrenal cortex extracts.

*Preparation.*—

Adrenal cortex extract is prepared by the method of Cartland and Kuizenga (*J. Biol. Chem.* 116:57, 1936). Frozen adrenal glands are extracted with chilled acetone and the gland residue removed by filtration. The acetone extract is concentrated in vacuo below 45 C. and the aqueous fraction so obtained is freed of inactive lipid substances by filtration and extraction with petroleum ether. The aqueous fraction is extracted with ethylene dichloride, which removes the adrenal cortex activity, leaving the epinephrine behind in the aqueous phase. Ethylene dichloride is removed in vacuo, and the residue is dissolved in alcohol and partitioned between 70 per cent alcohol and petroleum ether. The 70 per cent alcohol solution is concentrated in vacuo below 45 C., and sodium chloride is added to the aqueous residue to make 0.9 per cent. An inactive precipitate is removed by filtration. Alcohol is added to make 10 per cent, and the solution is sterilized by Berkefeld filtration.

Adrenal cortex extract is assayed biologically according to the Cartland and Kuizenga method (*Am. J. Physiol.* 117:678, 1936). Each cubic centimeter contains not less than 50 dog units (2.5 rat units) when

assayed according to the method of Cartland and Kuizenga. This assay method depends on the maintenance of life in adrenalectomized dogs. The epinephrine content of the extract as determined by the U. S. P. dog blood pressure method is less than 1:200,000.

#### THE UPTON COMPANY

**Solution Adrenal Cortex Extract:** 10 cc. vials. Each 1 cc. contains not more than 3 mg. of gland extractives, having a potency equivalent to 50 dog units when assayed by the Cartland-Kuizenga method, in physiological solution of sodium chloride. Preserved with 10 per cent of alcohol.

U. S. patent 2,053,549 (Sept. 8, 1936; expires 1953) and 2,096,342 (Oct. 19, 1937; expires 1954).

### *Adrenal Medulla*

(See Epinephrine in Chapter on Autonomic Drugs.)

### Ovaries

Sex hormones, as a rule, are closely related chemically. These compounds are also similar in structure to the steroids of the adrenal cortex. They possess, likewise, physiological properties common to each other. For instance, certain androgens possess estrogenic or progestational qualities while progesterone is said to have a slight androgenic activity in laboratory animals. The steroids of the adrenal cortex may account for the virilism, feminism or precocious puberty seen in patients with adrenal cortical tumors.

The ovaries produce internal secretions which are necessary for the proper functioning of the uterus, in particular, for the production of cyclic growth processes of the endometrium and for the development of the decidua; in addition these internal secretions determine cyclic changes in the vagina and cervix and influence the growth of the mammary gland. It is known that in addition to intrinsic factors situated in the ovary itself, hormones given off by the anterior pituitary regulate the growth of the follicles, ovulation, and corpus luteum formation.

The follicle stimulating hormone of the anterior pituitary induces growth of the ovarian follicles. During this period estrogenic hormone is secreted by the follicles (probably from the cells of the theca interna), which evokes certain changes in the accessory organs. The vaginal mucosa thickens and the cells undergo a more intense cornification; the myometrium hypertrophies, while the endometrium changes rather rapidly to the proliferative phase. At this time the duct system of the breast develops to a varying extent. After ovulation there is a release of the luteinizing hormone of the pituitary, and the collapse follicle becomes transformed into a corpus luteum which secretes progesterone. In the human the corpus luteum elaborates estrogenic hormone as well. The progestational hormone induces secretory changes in the endometrium preparatory

to nidation, and stimulates growth of the alveolar breast tissue. Menstruation results when the corpus luteum suddenly ceases to produce progesterone. Estrogen is also low at this time. The intrinsic factors which cause extravasation of blood and tissue fragmentation at the end of the cycle are not yet clear.

*Estrogen:* The injection of potent estrogenic substances in castrate animals will induce changes in the accessory sex organs which are typical of estrus. Long continued injections, however, induce hypertrophic then metaplastic changes in the uterus, cervix and breast. It is often considered that clinical endometrial hyperplasia, chronic cystic mastitis and fibromyomas are due to long continued estrogen secretion by the ovary.

Estrogenic substance is also responsible for the contractility of the uterus and the sensitivity of the myometrium to oxytocic agents. It has recently been shown that the smooth muscle of the human Fallopian tube is also responsive to estrogenic substance.

The excretion curve of estrogenic substances in the normally menstruating women is irregular and varies extremely from day to day. In general, however, there is at least one peak at the height of follicular activity at ovulation time. Excretion curves in ovarian disorders have not been adequately studied at the present time because of numerous technical difficulties in assays. During pregnancy large amounts of estrogens are excreted in the urine in the form of water soluble conjugate. In pregnant women these are in the form of glucuronides, and in pregnant mares in the form of sulfates. Hydrolysis of the urine, either by acid or by putrefaction, converts the conjugated estrogens into their free forms, which are more active physiologically.

Estrogenic substances occur widely in nature, in plants as well as in animals. Estrone (ketohydroxyestrin) and estriol (trihydroxyestrin) are extracted from pregnancy urine or placentas of humans while several estrogens, including estrone, equilin and hippulin, are obtained from the urine of pregnant mares. Sow's ovaries contain both estrone and estradiol (dihydroxyestrin), but not in sufficient quantities to make them a worthwhile source commercially. Estradiol exists in two stereoisomeric forms—alpha and beta. The alpha estradiol is probably the most potent of all known estrogens; the beta form is relatively inert. Since estrogens are relatively rapidly destroyed in the animal body, several estrogen compounds which are absorbed slowly from the site of injection may be more efficient. Fatty acid esters of the estrogens (benzoate, acetate, propionate, palmitate) have therefore been prepared to meet this purpose.

Estrogens are used either orally, intravaginally or by hypodermic injection of a solution in oil or a colloidal suspension in an aqueous solvent. Estrone and estradiol lose considerable activity when taken orally. When estrone is administered in the form of its sulfate, it appears to retain a greater amount of its potency. Several estrogenic compounds have been prepared which lose relatively little potency when administered orally.

Besides crystalline estrogens, preparations of highly purified but noncrystalline estrogens are available. These are usually extracted from the urine of pregnant women or pregnant mares; the estrogenic activity of such extracts is due almost entirely to estrone. The Council has coined the term Solution of Estrogens for such preparations.

There has been an enormous amount of clinical research with estrogenic substances. Claims for therapeutic results have been often exaggerated and confusing. Definite and consistently reliable results have been obtained in only a relatively small number of conditions. All other indications should be considered unscientific or in the experimental stage of therapy.

Estrogens are carcinogenic when administered experimentally to animals which have an inherited sensitivity to the development of mammary carcinoma. Many clinicians believe that estrogens are therefore contraindicated in the treatment of women who have a familial or personal history of mammary or genital malignancy. However, the current clinical observations on the use of estrogens in treatment of inoperable breast carcinoma must be considered. A limited, palliative effect may be obtained in older women, around 70 years, with breast cancer metastases of the soft tissues.

Estrogenic substances are used in a considerable variety of conditions associated with deficiency of estrogens. These include treatment of the symptoms of the menopause syndrome, natural or artificial, senile vaginitis, kraurosis vulvae, and pruritus vulvae. Some authorities suggest that sufficiently small doses of estrogens may be given to control vasomotor symptoms of the menopause without producing endometrial or vaginal epithelial changes. A related use is in the treatment of hypogonitalism in the female, but the use of estrogen in such conditions must be understood as substitution for ovarian function, not as stimulating such activity. Estrogens have been used in attempts to inhibit production of gonadotropic hormone by the anterior pituitary. This result requires very large doses. For a time it was thought that large doses of estrogen inhibited lactation immediately post partum. This is doubted, but estrogenic therapy has been found helpful in relieving the engorgement of breasts especially when lactation is to be suppressed.

It has been found possible to interrupt the prolonged or excessive flowing of many women with "functional bleeding" by brief courses of intensive estrogenic therapy. This is considered safe practice only when the interval of freedom from bleeding is used to eliminate local pelvic lesions as the cause of the flowing. The subsequent administration of sequences of estrogenic substances and progesterone to reestablish cycles of flowing is a possible method of alleviating a condition which is widely believed to result from deficiency of one or both of the ovarian hormones.

Estrogenic materials have been reported to act together with or as a substitute for castration in the palliation of the local

discomforts from prostatic carcinoma and its metastases. The action is apparently not curative but may persist for a number of months.

Estrogens cause uterine and vaginal growth and proliferation and frequently endometrial bleeding which are undesirable effects. Since the advent of effective antibiotics, the use of estrogens is no longer indicated in the treatment of gonorrheal vaginitis in children, except possibly in cases which are refractory to penicillin.

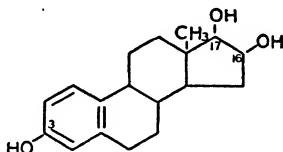
*Progesterone:* The hormone of the corpus luteum—induces secretory changes of the endometrium, stimulates growth of the mammary alveolar tissue and relaxes the uterine smooth muscle. It is essential for nidation of the ovum, and the maintenance of pregnancy. During gestation the ovary elaborates progesterone only through the third month, after which the placenta is responsible for its elaboration. Progesterone is not excreted as such, but in the form of pregnandiol glycuronide, and is found in the urine of pregnancy, or during the corpus luteum phase of the normal cycle. Studies on habitual abortion have revealed that pregnandiol excreted in the urine may be abnormally low at about the hundredth day of gestation, indicating an insufficiency of progesterone. It has been calculated that the administration of 10 mg. to 50 mg. of progesterone daily may be required to bring the pregnandiol level to normal.

A substance which has progestational activity when administered orally has recently appeared on the market. It is crystalline anhydro-hydroxy-progesterone. There is increasing evidence in the literature to indicate its therapeutic value at the present time.

Commercial preparations of progesterone are either extracts of animal ovaries, or the pure compound prepared synthetically. At one time there was considerable enthusiasm over the therapeutic use of such preparations in dysmenorrhea, menorrhagia and habitual abortion, but the volume of satisfactory evidence is too small to warrant dependence on progesterone for treatment of these conditions. The Council has not accepted progesterone or any preparation of this principle.

### Natural Estrogens

**ESTRIOL.**—Theelol. —  $C_{18}H_{24}O_3$ . — 3,16,17-trihydroxy- $\Delta$ -1,3,5-estratriene. A crystalline estrogenic steroid isolated from the urine of pregnancy. The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Estriol is used orally for the same conditions for which estrogenic substances are employed and its contraindications are similar to those of other estrogen. Estriol is much less actively estrogenic than estrone when injected. See general article under Estrogen.

*Dosage.*—Orally from 0.06 to 0.12 mg. from one to four times a day, alone or as supplement to parenteral therapy.

Estriol is manufactured under license from St. Louis University under U. S. patents 1,967,350 and 1,967,351 (July 24, 1934; expire 1951).

ABBOTT LABORATORIES

**Capsules Estriol:** 0.12 mg. and 0.24 mg.

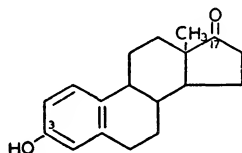
ELI LILLY AND COMPANY

**Pulvules Estriol:** 0.06 mg., 0.12 mg. and 0.24 mg.

PARKE, DAVIS & COMPANY

**Kapseals Theelol:** 0.24 mg.

**ESTRONE-U. S. P.**—Theelin. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Estrone.

*Actions and Uses.*—Estrone (theelin) is used for the same conditions for which estrogenic substances are employed and its contraindications are similar to those for other estrogens. See general article under Estrogen.

*Dosage.*—In disturbances of the menopause 0.2 mg. (2,000 I. U.) to 1.0 mg. (10,000 I. U.) injected intramuscularly one or more times weekly depending on the response of the patient. After producing relief, dosage may be lowered to a maintenance level. As much as 5.0 mg. (50,000 I. U.) per week may be required in resistant cases of kraurosis vulvae. Estrone suppositories are valuable adjuncts in the treatment of senile vaginitis.

Occasionally a considerable amount of uterine bleeding occurs in menopausal women following large doses of estrone. This may be quite alarming at times and it is, therefore, advisable to reduce the dose of estrone as soon as feasible.

Estrone is effective by mouth if the dosage is adequate.

Estrone is manufactured under license from St. Louis University under U. S. patents 1,967,350 and 1,967,351 (July 24, 1934; expire 1951).

## ABBOTT LABORATORIES

**Solution Estrone in Oil:** Ampuls 0.2 mg. in 1 cc. (2,000 international units); 0.5 mg. in 1 cc. (5,000 international units), and 1 mg. in 1 cc. (10,000 international units) in peanut oil.

**Solution Estrone in Oil:** 1 mg. 10,000 international units in peanut oil 10 cc. vials. Preserved with chlorobutanol 0.5 per cent.

**Aqueous Suspension Estrone:** 2 mg. in 1 cc. ampuls (20,000 international units). Each cubic centimeter contains estrone crystals 2 mg. in aqueous suspension with isotonic sodium chloride solution.

**Aqueous Suspension Estrone:** 1 mg. 10,000 international units and 5 mg. 50,000 international units per cc. ampuls. Each cubic centimeter contains estrone crystals in aqueous suspension with isotonic sodium chloride solution, stabilized with acacia.

**Vaginal Suppositories Estrone:** 0.2 mg. in a glycerogelatin base.

## ELI LILLY AND COMPANY

**Aqueous Suspension Estrone:** 1 mg., 2 mg. 5 mg. per cc., 1 cc. ampuls.

**Solution Estrone in Oil:** Ampuls 0.1 mg. in 1 cc. (1,000 international units); 0.2 mg. in 1 cc. (2,000 international units); 0.5 mg. in 1 cc. (5,000 international units), and 1 mg. in 1 cc. (10,000 international units) in cotton seed oil.

**Vaginal Suppositories Estrone:** 0.2 mg. (2,000 international units) in a glycerin base.

## PARKE, DAVIS &amp; COMPANY

**Solution Theelin in Oil:** Ampuls 0.1 mg. in 1 cc. (1,000 international units); 0.2 mg. in 1 cc. (2,000 international units); 0.5 mg. in 1 cc. (5,000 international units), and 1 mg. in 1 cc. (10,000 international units) in peanut oil.

**Solution Theelin in Oil:** 1 mg. (10,000 international units) in 10 cc. vials in peanut oil.

**Aqueous Suspension Theelin:** 2 mg. in 1 cc. ampuls (20,000 international units).

**Aqueous Suspension Theelin:** 1 mg. (10,000 international units) and 5 mg. (50,000 international units) in 1 cc. ampuls.

**Vaginal Suppositories Theelin:** 0.2 mg. (2,000 international units) in glycerogelatin base.

**ESTROGENIC SUBSTANCES (*Water Insoluble*).—Amniotin-Squibb.**—A highly concentrated, noncrystalline preparation of estrone (ketohydroxyestrin) together with a small

varying amount of other estrogenic phenolic ketones extracted from the urine of pregnant mares.

*Actions and Uses.*—Estrogenic substances are used for the same condition for which all estrogens are employed and their contraindications are similar. See the general article under Estrogen.

*Dosage.*—From 2,000 to 20,000 international units injected one or more times weekly depending on the response of the patient. After relief has been produced, dosage may be lowered to a maintenance level. As much as 15,000 international units per week may be required in resistant cases of kraurosis vulvae. Suppositories of estrogenic substances are valuable adjuncts in the treatment of senile vaginitis.

Occasionally a considerable amount of uterine bleeding occurs in menopausal women following large doses of any estrogenic substance. This may be quite alarming at times and it is therefore suggested that the dose be reduced as soon as feasible.

Capsules or tablets of estrogenic substances, 1,000, 2,000, 4,000 or 10,000 international units, one or more times daily, may be administered orally alone or as a supplement to parenteral therapy.

#### *Preparation.*—

Urine from pregnant mares, collected after the fifth month of pregnancy, is acidified with hydrochloric acid to pH 1.5 and boiled for three hours. The hydrolyzed urine is extracted with ethylene dichloride, and the extract evaporated to dryness. The residue is dissolved in ether, the ether solution is washed with half saturated sodium carbonate solution, followed by tenth normal sodium hydroxide and finally the ether removed by distillation. This residue is dissolved in toluene and the active material is extracted from the toluene with normal sodium hydroxide. This alkaline extract, after neutralization with hydrochloric acid, is extracted with toluene, and the toluene solution, after washing with water, is evaporated to dryness.

This residue is further purified by high vacuum fractional distillation. The resulting residue is dissolved in sterile vegetable oil for hypodermic and oral use and incorporated in a glycerogelatin base for vaginal administration.

Estrogenic substances are assayed by a modification of the Coward and Burn method in direct comparison with the international standard. The potency is expressed in terms of the international unit. One international unit is defined by the League of Nations Health Organization as the specific estrus producing activity contained in 0.1 microgram (0.0001 mg.) of the standard crystalline ketohydroxy estrin ( $C_{18}H_{22}O_2$ ). The physiologic criterion of activity is the appearance of cornified cells in the vaginal smear of a castrated rat.

BARRY BIOLOGICAL LABORATORY, DIVISION OF BARRY LABORATORIES, INC.

**Solution Estrogenic Hormones in Oil:** 30 cc. and 100 cc. vials containing the equivalent of 10,000 international units per cubic centimeter of estrone in sesame oil with chlorobutanol 0.5 per cent as a preservative.

GEORGE A. BREON & COMPANY, INC.

**Solution Estrogenic Substances in Oil:** 1 cc. ampuls available as 2,000 international units per cc., 5,000 international units



per cc., 10,000 international units per cc. of estrogenic substances in sesame oil.

**Solution Estrogenic Substances in Oil with Chlorobutanol 3% :** 10 cc. vials. Each cubic centimeter contains 10,000 and 20,000 international units of estrogenic substance in sesame oil.

**Solution Estrogenic Substances in Oil with Chlorobutanol 3% :** 30 cc. vials containing the equivalent of 10,000 international units per cubic centimeter in sesame oil. Preserved with 3 per cent chlorobutanol.

BRISTOL LABORATORIES, INC.

**Solution Estrogenic Substances in Oil with Benzyl Alcohol 3% :** 1 cc. size ampul containing the equivalent of 2,000 international units per cubic centimeter, 5,000 international units per cubic centimeter, 10,000 international units per cubic centimeter or 20,000 international units per cubic centimeter of estrone in sesame oil.

**Solution Estrogenic Substances in Oil with Benzyl Alcohol 3% :** 10 cc. and 30 cc. vials, each being available in potencies containing the equivalent of 2,000 international units per cubic centimeter, 5,000 international units per cubic centimeter, 10,000 international units per cubic centimeter or 20,000 international units of estrone per cubic centimeter in sesame oil.

ENDO PRODUCTS, INC.

**Aqueous Suspension Estromone:** 20,000 international units per cc., 1 cc. ampuls, 5 cc. and 10 cc. vials. Preserved with phenol 0.5 per cent and tri-isopropanolamine 0.5 per cent, in solution sodium chloride 0.9 per cent.

**Solution Estromone in Oil:** 1 cc. ampuls and 10 and 25 cc. vials. Each cubic centimeter contains estrogenic substances equivalent to 2,000, 5,000, 10,000 or 20,000 international units of estrone in sesame oil. The 10 cc. and 25 cc. vials contain 0.5 per cent chlorobutanol as preservative.

**Tablets Estromone:** 1,000 international units, 2,000 international units and 4,000 international units.

U. S. trademark 345,724. May 4, 1937.

FORBES LABORATORIES

**Solution Estrogenic Substances in Oil:** 10,000 international units 1 cc. ampuls, 10 cc., 30 cc. vials; 20,000 international units in sesame oil 1 cc. ampuls, 10 cc. and 20 cc. vials. Preserved with chlorobutanol 0.5 per cent.

LAKESIDE LABORATORIES, INC.

**Aqueous Suspension Estrogenic Substances:** 1 cc. ampuls and 5 cc. vials. A sterile suspension, each cubic centimeter of

which contains estrogenic substances (water insoluble) equivalent to 20,000 international units of estrone, in isotonic solution of sodium chloride.

**Solution Estrogens in Oil:** 1 cc. ampuls available as 2,000 international units per cc., 5,000 international units per cc., 10,000 international units per cc. and 20,000 international units per cc.; 10 cc. rubber stoppered vials containing per cc. the equivalent of 20,000 international units; 15 cc. rubber stoppered vials containing per cc. 5,000 international units and 10,000 international units, and 25 cc. rubber stoppered vials containing per cc. the equivalent of 2,000 international units in sesame oil. Chlorobutanol 0.5 per cent is added as a preservative.

**Tablets Estrogens:** 1,000 international units, 2,000 international units and 4,000 international units.

LINCOLN LABORATORIES, INC.

**Aqueous Suspension Estrogenic Substances:** 1 cc. ampuls containing 10,000 or 20,000 international units per cubic centimeter, 5 cc. vials containing 50,000 international units per cubic centimeter and 15 cc. vials containing 10,000 or 20,000 international units per cubic centimeter. Estrogenic substances (water insoluble) is suspended in isotonic sodium chloride solution containing 2 per cent benzyl alcohol as a local anesthetic with 0.1 per cent pectin and 0.05 per cent sodium oleate as suspending agents. Phenol 0.5 per cent is added as a preservative.

**Solution Estrogenic Substances in Oil with Benzyl Alcohol 2%:** 1 cc. ampuls and 15 cc. vial available as 5,000 international units per cubic centimeter, 10,000 international units per cubic centimeter and 20,000 international units per cubic centimeter in sesame oil. Preserved with chlorobutanol 0.5 per cent.

E. S. MILLER LABORATORIES, INC.

**Solution Estrogenic Substances in Oil:** 1 cc. ampuls and 10 cc. and 30 cc. vials, each being available in potencies containing the equivalent of 5,000 international units per cubic centimeter or 10,000 international units per cubic centimeter; 10 cc. and 30 cc. vials being available in potencies containing the equivalent of 20,000 international units per cubic centimeter of estrone in a neutral vegetable oil, with benzocaine 2 per cent. Preserved with cresol 0.5 per cent.

REED & CARNICK

**Solution Estrogenic Substances in Oil:** 1 cc. ampuls and 5 cc., 10 cc. and 20 cc. vials available as 2,000 international units per cubic centimeter, 6,000 international units per cubic centimeter, 10,000 international units per cubic centimeter and 25,000 international units per cubic centimeter in peanut oil. Preserved with chlorobutanol 0.5 per cent.

**Tablets Estrogenic Substances:** 1,000 international units and 5,000 international units.

**SHARP & DOHME, INC.**

**Capsules Estrogenic Substances in Oil:** 1,000 international units, 2,000 international units or 4,000 international units of estrone in peanut oil.

**Solution Estrogenic Substances in Oil:** 1 cc. size ampuls containing the equivalent of 2,000 international units per cubic centimeter, 5,000 international units per cubic centimeter or 10,000 international units of estrone per cubic centimeter in peanut oil.

**SMITH-DORSEY COMPANY**

**Solution Estrogenic Substances in Oil:** 1 cc. ampuls, available as 2,000 international units per cc., 5,000 international units per cc. and 10,000 international units per cc., and 10 cc. ampul-vial available as 5,000 international units, 10,000 international units and 20,000 international units in peanut oil. Chlorobutanol 0.5 per cent is added as a preservative.

**Solution Estrogenic Substances in Oil with Benzyl Alcohol 3%:** 1 cc. ampuls available as 5,000 international units per cubic centimeter, 10,000 international units per cubic centimeter and 20,000 international units per cubic centimeter and 10 cc. ampul-vials available as 10,000 international units per cubic centimeter and 20,000 international units per cc. in peanut oil.

**Solution Estrogenic Substances in Oil with Benzyl Alcohol 3%:** 1 cc. ampul containing the equivalent of 2,000 international units per cc., 5,000 international units per cc. and 10,000 international units per cc. of estrone; 10 cc. ampuls containing in each cc. the equivalent of 20,000 international units of estrone with 3 per cent benzyl alcohol added as a preservative, and 10 cc. ampul-vial containing in each cc. the equivalent of 10,000 international units of estrone in sesame oil.

**CARROLL DUNHAM SMITH PHARMACAL CO.**

**Aqueous Suspension Estrusol:** 20,000 international units per cc. in isotonic sodium chloride solution, 1 cc. ampuls, 5 cc. and 15 cc. vials. Vials preserved with chlorobutanol 0.5 per cent.

**Aqueous Suspension Estrusol:** 1 cc. Dual syringe cartridges available as 20,000 international units per cubic centimeter. Each cubic centimeter contains isotonic sodium chloride suspension of estrogenic substances, principally estrone, with small amounts of other natural estrogens. Preserved with chlorobutanol 0.5 per cent.

**Solution Estrusol in Oil:** 2,000, 5,000 and 10,000 international units per cc. in peanut oil 1 cc. ampuls, 2,000 and 10,000

international units per cc. in peanut oil 15 cc. vials. Preserved with chlorobutanol 0.5 per cent.

**Solution Estrusol in Oil with Benzyl Alcohol 3%:** 20,000 international units per cc. in peanut oil, 1 cc. ampuls, and 5 cc. and 15 cc. vials.

E. R. SQUIBB & SONS

**Capsules Amniotin:** 1,000 international units, 2,000 international units, 4,000 international units and 10,000 international units.

**Pessaries Amniotin:** 2,000 and 5,000 international units. Each pessary contains sufficient estrogenic substances (water insoluble) in corn oil to provide the stated unitage expressed in terms of estrone, enclosed in a soft gelatin capsule for use as a vaginal suppository.

**Solution Amniotin in Oil:** 1 cc. size ampuls containing 2,000 international units per cc., 5,000 international units per cc., 10,000 international units per cc. and 20,000 international units per cc.; 10 cc. vials containing 10,000 international units per cc. or 20,000 international units per cc., and 20 cc. vial containing 2,000 international units per cc. in corn oil.

U. S. trademark 318,536.

WARREN-TEED PRODUCTS COMPANY

**Solution Estrovarin in Oil:** 15 cc. vials. Each cubic centimeter contains estrogenic substances equivalent to 10,000 international units of estrone in sesame oil, with chlorobutanol 0.5 per cent as a preservative.

**ESTROGENIC SUBSTANCES (Water Soluble).—**  
**Conestron-Wyeth.—Premarin-Ayerst.**—An amorphous preparation containing the naturally occurring, water soluble, conjugated forms of the mixed estrogens obtained from the urine of pregnant mares.

The principal estrogen present in estrogenic substances (water soluble) is sodium estrone sulfate. Varying small amounts of other equine estrogens and relatively large quantities of non-estrogenic material are also present in the mixture. The total estrogenic potency of the preparation is expressed in terms of an equivalent quantity of sodium estrone sulfate.

**Actions and Uses.**—Water soluble estrogenic substances are used in the same conditions for which other estrogenic substances are employed and the contraindications are those for other estrogens. See general article under Estrogen.

**Dosage.**—For the control of menopausal symptoms, 1.25 mg. is usually sufficient. If after a few days of treatment the response is not satisfactory, the dose may be increased. After symptoms have been brought under control the dosage can usually be

reduced. For the treatment of senile vaginitis, kraurosis vulvae and pruritus vulvae, 1.25 to 3.75 mg. daily should be sufficient.

*Preparation.*—

Estrogenic substances (water soluble) may be prepared in the following manner: To fresh urine from mares pregnant five months or longer, sufficient xylene is added to prevent hydrolysis of conjugated estrogens. The urine is then concentrated under reduced pressure at 40 to 50 C., the pH being maintained at or near neutrality. The urine concentrate is extracted several times with water-saturated butyl alcohol. The butyl alcohol extracts are washed several times with tenth-normal sodium hydroxide, then twice with small volumes of water and then concentrated to a small volume under reduced pressure at 40 to 50 C.

The concentrate is taken up in acetone and, after the insoluble material has been removed, the acetone solution is concentrated to a small volume. The acetone concentrate is treated with an excess of ether and the precipitate obtained is removed and dried. This precipitate, which varies in color from reddish brown to almost white, is an amorphous, hygroscopic powder possessing a characteristic odor. It is soluble in water, dissolving freely to form a pale yellow solution; soluble in alcohol and acetone; insoluble in benzene and ether.

Estrogenic substances (water soluble) may also be removed from the urine of pregnant mares by selective adsorption and elution. The eluate may be purified by solvent partition and finally reduced to powder in a vacuum dryer.

Estrogenic substances (water soluble) are assayed chemically by a modification of the phenol sulfonic acid colorimetric method introduced by Kober and biologically by oral administration to adult ovariectomized rats, using the technic of Kahnt and Doisy. The standard of reference for the chemical assay is the international standard for estrone. This standard being inapplicable to the biologic assay of conjugated estrogens, in the rat assay biologic variation is controlled by the use of a house standard preparation of conjugated estrogens.

AYERST, MCKENNA & HARRISON, LTD.

**Premarin (Liquid):** 120 cc. bottles. Each 4 cc. contains 0.625 mg. of estrogenic substances (water soluble) and 12.5 per cent alcohol.

U. S. trademark 397,925.

**Tablets Premarin:** 0.63 mg., 1.25 mg. and 2.5 mg.

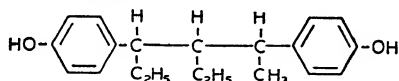
WYETH, INC.

**Tablets Conestron:** 1.25 mg., and 0.625 mg.

U. S. trademark pending.

### *Synthetic Estrogens*

**BENZESTROL.**—2,4-Di(*p*-hydroxyphenyl)-3-ethyl hexane. —Benzestrol is one pair of racemates of the synthetic substance possessing the following structural formula:



For tests and standards, see Section B.

**Actions and Uses.**—This compound when introduced into the human body orally and by injection provokes a response similar

to that caused by other estrogenic substances. See general article under Estrogen. It is claimed to have a low incidence of toxicity. Contraindications are similar to those of other estrogens.

**Dosage.**—By biologic assay, 1 mg. of benzenestrol is reported to be equivalent to approximately 25,000 international units or to 1,250 rat units of estrone. Average dose in tablets is about 2 or 3 mg. and in injection from 2 to 5 mg. This may be repeated daily for four to seven days until the dosage requirement is determined by clinical observation.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Solution Benzenestrol in Oil:** 5 mg. per cc. 10 cc. vials. Preserved with 0.5 per cent chlorobutanol in sesame oil.

**Tablets Benzenestrol:** 2 mg. and 5 mg.

SCHIEFFELIN & Co.

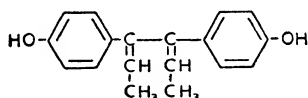
**Elixir Benzenestrol:** 473 cc. bottles. Each 4 cc. contains benzenestrol 2 mg. in a sweetened aromatic elixir containing alcohol 25 per cent.

**Solution Benzenestrol:** 10 cc. multiple dose, rubber capped vials, 5 mg. per cc.

**Tablets Benzenestrol:** 0.5 mg., 1.0 mg., 2.0 mg. and 5.0 mg.

**Vaginal Tablets Benzenestrol:** 0.5 mg.

**DIENESTROL.** — 3,4-bis(*p*-hydroxyphenyl)-2,4-hexadiene. —The structural formula of dienestrol may be represented as follows:



For tests and standards see Section B.

**Actions and Uses.**—Dienestrol is used orally for the same conditions for which estrogenic substances are employed, and its contraindications are similar to those of other estrogens.

**Dosage.**—In the treatment of menopausal symptoms, orally in daily doses of 0.1 to 0.5 mg. for mild to moderately severe symptoms. In artificially induced climacteric a daily dosage of 0.5 to 1.5 mg. may be necessary.

For suppression of lactation a dose of 0.5 mg. three times a day for the first three days and 0.5 mg. daily thereafter for one week is the dosage usually employed.

RARE CHEMICALS, INC.

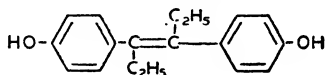
**Tablets Dienestrol:** 0.1 mg. and 0.5 mg.

WHITE LABORATORIES, INC.

Tablets Dienestrol: 0.1 mg. and 0.5 mg.

**DIETHYLSTILBESTROL-U. S. P.**—Stilbestrol.— $\alpha$ - $\alpha'$ -diethyl-4-4'-stilbenediol. — 3,4-*bis*-(*p*-hydroxyphenyl)-3-hexene. —“When dried for 4 hours at 100 C. contains not less than 98.5 per cent of  $C_8H_{20}O_2$ .”—*U. S. P.*

Diethylstilbestrol has the following structural formula:



For description and standards see the U. S. Pharmacopeia under Diethylstilbestrol, Diethylstilbestrol Capsules, Diethylstilbestrol Injection and Diethylstilbestrol Tablets.

**Actions and Uses.**—Dodds and his co-workers, after extensive experimentation with synthetic substances, recognized the estrogenic activity of the stilbene compounds. Diethylstilbestrol is the most potent of these compounds described up to the present time. It may be prepared in a variety of ways from nonbiologic, organic chemicals. Its physiologic activity duplicates practically all the known actions of natural estrogens. Thus it induces estrus in rodents, stimulates the growth of the endometrium and myometrium, primes the endometrium for progestational changes, causes reddening of the “sex skin” of monkeys and feminization of the plumage of birds, induces growth of mammary ducts in female and male animals as well as in human beings, raises the blood fat and calcium in fowl, induces uterine bleeding in castrate animals and human beings and suppresses ovulation as well as inhibits the secretion of various factors of the anterior pituitary gland, resulting in stunting of growth, inhibition of lactation and atrophy of the gonads. It differs in its action from natural estrogens in its inability to cause the ovipositor reaction of the female bitterling and to antagonize the action of androgens on comb growth of capons. The therapeutic use has been demonstrated to be effective for all those conditions recognized to respond to the natural estrogens. Various modifications of diethylstilbestrol have been devised, such as fatty acid esters and a number of ethers, for increasing the estrogenic efficiency of this substance. These are at present the subject of clinical and physiologic investigations. Diethylstilbestrol possesses the advantage of being highly active by mouth as well as percutaneously. The ratio of potency between oral and parenteral administration varies in the hands of different investigators from 1:2 to 1:5 in the human being as well as in rodents. In the therapeutic use of diethylstilbestrol there may be a significant incidence of side reactions, the most common of these being nausea, vomiting and headache. It has been considered that these were the result of tissue damage, but no evidence has been presented that therapeutic amounts are actually harmful to human beings and there appears to be conclusive evidence that

experimentally diethylstilbestrol is not significantly more toxic than the natural estrogens. It is now considered that the unpleasant symptoms arising from diethylstilbestrol administration are systemic in origin rather than local, probably because of its rapid absorption into the blood stream, since few untoward symptoms are observed with the use of diethylstilbestrol compounds, which are slowly absorbed from the site of administration.

Diethylstilbestrol is used for the same conditions for which estrogenic substances are employed and the contraindications are those of the natural estrogens. See general article under Estrogen.

**Dosage.**—The average therapeutic dose for the treatment of menopausal symptoms is 0.5 to 1.0 mg. daily by mouth, although it is advised to start with smaller doses for patients who tend to develop disagreeable symptoms. For the suppression of lactation 5 mg. once or twice daily for a total of from two to four days has been recommended. Courses of therapy with periods of a few weeks of no treatment are recommended by some authorities. Injection of similar quantities of diethylstilbestrol in oil solution are administered one or more times weekly. Ointment or suppositories containing this material may be used for topical applications in the treatment of vulvar and vaginal conditions. In prostatic carcinoma, the recommended dosage is 3 mg. daily intramuscularly for several weeks, after which the dosage is gradually reduced to 1 mg. daily.

#### ABBOTT LABORATORIES

**Solution Diethylstilbestrol in Oil:** 0.5 mg., 1.0 mg. and 5 mg. per cc., 1 cc. ampuls in peanut oil.

**Tablets Diethylstilbestrol:** 0.1 mg., 0.25 mg., 0.5 mg., 1 mg. and 5 mg.

**Vaginal Suppositories Diethylstilbestrol:** 0.5 mg.

#### BIO-INTRASOL LABORATORIES, INC.

**Solution Diethylstilbestrol in Oil:** 1.0 mg. per cc. in sesame oil, 1 cc. ampuls.

#### GEORGE A. BREON & COMPANY, INC.

**Caplets Diethylstilbestrol:** 0.2 mg., 0.5 mg., 1 mg. and 5.0 mg.

**Solution Diethylstilbestrol in Oil:** 1.0 mg. per cc., 1 cc. ampuls.

#### COLE CHEMICAL Co.

**Tablets Diethylstilbestrol:** 1 mg.

**Solution Diethylstilbestrol in Oil:** 1 mg. per cc. in peanut oil, 1 cc. ampuls.



## THE DRUG PRODUCTS CO., INC.

**Hyposols Diethylstilbestrol in Oil:** 0.5 mg., 1 mg. and 5 mg., 1 cc. ampuls in sesame oil.

**Hyposols Diethylstilbestrol in Oil:** 0.5 mg. and 1 mg. per cc., 30 cc. vials and 5 mg. per cc., 10 cc. vials in sesame oil with 0.5 per cent chlorobutanol anhydrous.

**Pulvoids Diethylstilbestrol:** 0.1 mg. and 1 mg.

## ENDO PRODUCTS, INC.

**Solution Diethylstilbestrol in Oil:** 0.5 mg., 1.0 mg., 2.0 mg. and 5.0 mg. per cc., 1 cc. ampuls in sesame oil.

## ESTRO CHEMICAL CO., INC.

**Solution Diethylstilbestrol in Oil:** 1 mg., 2 mg., and 5 mg. per cc., 1 cc. ampuls and 30 cc. vials in corn oil. Preserved with chlorobutanol 0.5 per cent.

## THE HARROWER LABORATORIES, INC.

**Solution Diethylstilbestrol in Oil:** 1.0 mg. per cc.: 1 cc. ampuls, and 5.0 mg. per cc., 10 cc. vials, preserved with 0.5 per cent chlorobutanol in peanut oil.

## KREMERS-URBAN CO.

**Tablets Diethylstilbestrol:** 1 mg. and 5 mg.

## ELI LILLY AND COMPANY

**Solution Diethylstilbestrol in Oil:** 0.25 mg., 0.5 mg., 1 mg. and 5 mg. per cc., 1 cc. ampuls in cottonseed oil.

**Suppositories Diethylstilbestrol:** 0.1 and 0.5 mg.

**Tablets Diethylstilbestrol:** 0.1 mg., 0.25 mg., 0.5 mg., 1 mg. and 5 mg.

## THE WM. S. MERRELL COMPANY

**Tablets Diethylstilbestrol:** 1.0 mg. and 0.25 mg.

## E. S. MILLER LABORATORIES, INC.

**Solution Diethylstilbestrol in Oil with Benzocaine 2%:** 0.5 mg. per cc., in sesame oil with Benzocaine 2 per cent, 1 cc. ampuls. Preserved with cresol 0.5 per cent.

**Tablets Diethylstilbestrol:** 0.1 mg., 0.5 mg. and 1.0 mg.

## PREMO PHARMACEUTICAL LABORATORIES, INC.

**Solution Diethylstilbestrol in Oil:** 0.2 mg., 0.5 mg., 1.0 mg. and 5.0 mg., 1 cc. ampuls in peanut oil.

**Tablets Diethylstilbestrol:** 0.1 mg., 0.5 mg., 1.0 mg. and 5.0 mg.

**Vaginal Suppositories Diethylstilbestrol:** 0.1 mg. and 0.5 mg.

**WILLIAM H. RORER, INC.**

**Solution Diethylstilbestrol in Oil:** 0.5 mg. and 1 mg. per cc., 1 cc. ampuls in peanut oil.

**Tablets Diethylstilbestrol:** 0.25 mg., 1 mg. and 5 mg.

**CARROLL DUNHAM SMITH PHARMACAL Co.**

**Solution Diethylstilbestrol in Oil:** 1.0 mg. per cc., 1 cc. ampuls in peanut oil.

**Tablets Diethylstilbestrol:** 0.1 mg., and 5.0 mg.

**SMITH-DORSEY COMPANY**

**Solution Diethylstilbestrol in Oil:** 0.5 mg. and 1 mg. per cc., 1 cc. ampuls in persic oil.

**Tablets Diethylstilbestrol:** 0.5 mg. and 1 mg.

**E. R. SQUIBB & SONS**

**Tablets Diethylstilbestrol:** 0.25 mg., 0.1 mg., 0.5 mg., 1.0 mg. and 5.0 mg.

**THE UPJOHN COMPANY**

**Perles Diethylstilbestrol:** 0.1 mg., 0.25 mg., 0.5 mg., 1.0 mg. and 5.0 mg.

**Solution Diethylstilbestrol in Oil:** 0.5 mg. and 1.0 mg. per cc., 1 cc. ampuls in cottonseed oil.

**Solution Diethylstilbestrol in Oil:** 0.5 mg. per cc., 20 cc. vials in cottonseed oil.

**THE VALE CHEMICAL Co., INC.**

**Tablets Diethylstilbestrol:** 0.1 mg., 0.5 mg. and 1.0 mg.

**WARREN-TEED PRODUCTS COMPANY**

**Solution Diethylstilbestrol in Oil:** 1 mg. per cc., 15 cc. vials containing 0.5 per cent chlorobutanol in sesame oil.

**Tablets Diethylstilbestrol:** 0.5 mg. and 1 mg.

**WINTHROP-STEARNs, INC.**

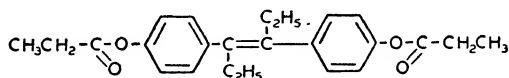
**Solution Diethylstilbestrol in Oil:** 0.5 mg. and 1 mg. per cc., 1 cc. ampuls in sesame oil.

**Suppositories Diethylstilbestrol:** 0.1 mg. and 0.5 mg.

**Tablets Diethylstilbestrol:** 0.1 mg., 0.5 mg., 1 mg. and 5 mg.

**DIETHYLSTILBESTROL DIPROPIONATE.**—The *di*-propionyl ester of  $\alpha,\alpha'$ -diethyl-4,4'-stilbenediol.—Diethylstilbestrol dipropionate may be prepared by esterification of diethyl-

stilbestrol with propionic acid chloride and purified by recrystallization from alcohol. It may be represented by the following structural formula:



For tests and standards, see Section B.

**Actions and Uses.**—Diethylstilbestrol dipropionate is used for the same conditions for which estrogenic substances are employed, although it is claimed that reactions such as nausea and vomiting appear to be less frequent with a dipropionate salt than with free diethylstilbestrol when the drugs are administered intramuscularly in oil. Diethylstilbestrol dipropionate is relatively slowly absorbed from the oil depot and causes a lower blood stream concentration, although one of more prolonged duration.

**Dosage.**—Diethylstilbestrol Dipropionate in Oil is administered intramuscularly, with the ratio of potency between oral and parenteral administration varying from 1:2 to 1:5. The following average dosages should be modified to meet individual requirements:

Menopause            { from 0.5 to 2 mg. intramuscularly two or  
Senile vaginitis    } three times a week.

Suppression of lactation—5 mg. intramuscularly once or twice daily for a total of from two to four days.

Carcinoma of the Prostate.—3 mg. intramuscularly daily for about ten days.

After a therapeutic effect has been obtained, the dosage should be reduced until the minimum effective dose for maintenance has been established.

#### THE BLUE LINE CHEMICAL COMPANY

**Solution Diethylstilbestrol Dipropionate in Oil:** 1.0 mg. per cc. in peanut oil, 1 cc. ampuls and 10 cc. vials.

**Tablets Diethylstilbestrol Dipropionate:** 0.1 mg., 1.0 mg. and 5.0 mg.

#### GEORGE A. BREON & Co., INC.

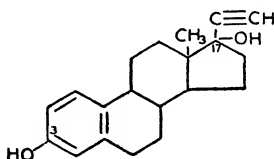
**Caplets Diethylstilbestrol Dipropionate:** 0.2 mg., 0.5 mg., 1.0 mg. and 5.0 mg.

**Solution Diethylstilbestrol Dipropionate in Oil:** 1.0 mg. per cc. in 1 cc. ampuls in sesame oil.

#### WINTHROP-STEARNs, INC.

**Solution Diethylstilbestrol Dipropionate in Oil:** 0.5 mg. per cc., 1 mg. per cc. and 5 mg. per cc., 1 cc. ampuls in olive oil.

**ETHINYL ESTRADIOL.**—Estinyl-Schering.—Ethinyl Estradiol. —17-ethinyl-3,17-dihydroxy- $\Delta$ -1,3,5-estratriene. — $C_{20}H_{24}O$ .—A crystalline, synthetic estrogenic derivative of  $\alpha$ -estradiol, possessing the following structural formula:



For tests and standards, see Section B.

Ethinyl estradiol may be prepared by the action of potassium acetylide upon estrone in liquid ammonia, followed by evaporation of the ammonia, solution in water and precipitation with mineral acid. The product is purified by recrystallization from methanol. When assayed biologically in rats by the Allen-Doisy method, ethinyl estradiol exhibits a potency of approximately 100,000 I.U. per milligram.

*Actions and Uses.*—The ethinyl radicle delays the decomposition of the estradiol molecule in the stomach, intestine, and liver, so that the drug can be given orally; it is one of the most potent estrogens known. In the female it compensates for deficiencies in estrogen production; in the male it opposes some of the actions of the androgens, as in **prostatic carcinoma**.

*Dosage.*—In hypo-ovarianism, three 0.05 mg. tablets daily by mouth are stated to be adequate for most patients. At the menopause, one 0.05 mg. tablet per day may be needed at first, but 0.02 mg. per day generally suffice for maintenance.

For functional uterine bleeding (menometrorrhagia) the suggested course consists of three cycles exactly alike. The first cycle begins as soon as the diagnosis is made, and consists of 20 days of treatment, 5 days of latent period, and 5 days of bleeding-episode, making a total of 30 days. From the first to the 15th day the daily treatment is six 0.05 mg. tablets of ethinyl estradiol alone. From the 16th to the 20th day the patient receives a daily intramuscular injection of 5 mg. of progesterone in addition to the daily dose of six 0.05 mg. tablets of ethinyl estradiol. The treatments are then suspended, and after a latent period of about five days the patient generally begins to bleed. Five additional days are allowed for this bleeding-episode, whereupon one begins the second cycle of treatments.

In prostatic carcinoma, the recommended dosage is three 0.05 mg. tablets daily for several weeks, after which the dosage is gradually reduced to one tablet daily. The incidence of side reactions, such as headache, nausea, and vomiting, is found in the same proportion of patients as occurs with other orally active estrogens.

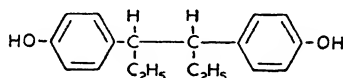
## SCHERING CORPORATION

**Estinyl (Liquid):** 120 cc. and 480 cc. bottles. Each 4 cc. contains ethinyl estradiol 0.03 mg. in syrup of cherry N. F. with 20 per cent alcohol.

**Tablets Estinyl:** 0.02 mg. and 0.05 mg.

U. S. patent's 2,251,939 and 2,265,976. U. S. trademark 398,209.

**HEXESTROL.** — *Meso-3,4-di-parahydroxyphenyl-n-hexane*. Hexestrol may be represented by the following structural formula:



It may be prepared from anethole in ether solution by (a) treating with anhydrous hydrogen bromide to form anethole hydrobromide, (b) conversion of the anethole hydrobromide to 3,4-dianisylhexane by means of metallic magnesium, aluminum, copper or zinc turnings and (c) hydrolysis of the 3,4-dianisylhexane to form hexestrol. The product thus obtained may be purified by recrystallization from dilute alcohol.

For tests and standards, see Section B.

**Actions and Uses.**—Hexestrol is used for the same conditions for which estrogenic substances are employed and the contraindications are those for natural estrogens. See general article under Estrogen. It is claimed to cause a lower incidence of toxic symptoms than those which follow diethylstilbestrol administration.

**Dosage.**—As is the case with all estrogenic substances, the dosage of Hexestrol must be adjusted to the individual case. As a guide the following dosages may be satisfactory: For menopausal symptoms, 2.0 to 3.0 mg. daily by mouth until symptoms are under control, and then 0.2 to 1.0 mg. daily as a maintenance dose; or by injection, 1.0 mg. in oil three times weekly with similar lowering for maintenance of control. For senile vaginitis and kraurosis vulvae, 2 to 3 mg. daily by mouth, or 1 mg. in oil three times weekly by injection. For suppression of lactation, 15.0 mg. one to three times daily for two or more days, or 15.0 mg. in oil daily for two or more days by injection.

S. E. MASSENGILL CO.

**Tablets Hexestrol:** 3 mg.

THE WM. S. MERRELL COMPANY

**Tablets Hexestrol:** 0.2 mg., 1.0 mg. and 3.0 mg.

THE WM. S. MERRELL CO., LOESER LABORATORY DIVISION

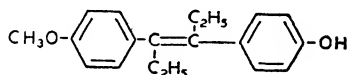
**Solution Hexestrol in Oil:** 1 mg. per cc., 20 cc. vials. Preserved with 0.5 per cent chlorobutanol in vegetable oil.

**Solution Hexestrol in Oil:** 5 mg. per cc., 20 cc. vials. Preserved with 0.5 per cent chlorobutanol in vegetable oil.

ORTHO PRODUCTS, INC.

**Tablets Hexestrol:** 1 mg. and 3 mg.

**MESTILBOL.**—**Monomestrol-Wallace & Tiernan.**—Diethylstilbestrol monomethyl ether. — 3-*p*-Hydroxyphenyl-4-*p*-methoxyphenyl-3-hexene. —  $\alpha,\alpha'$ -Diethyl-4'-methoxy-4-stilbenol. —Mestilbol may be represented by the following structural formula:



It may be prepared by methylation of diethylstilbestrol or by partial demethylation of the dimethyl ether of diethylstilbestrol. The crude product may be purified by distillation in vacuum and recrystallization from water-alcohol or from benzene-petroleum ether mixtures.

For tests and standards, see Section B.

**Actions and Uses.**—Mestilbol is used for the same conditions for which estrogenic substances are employed, and the contraindications are essentially the same. Like other estrogens, it must be individualized since each patient presents special problems. Patients undergoing treatment should remain under constant medical supervision. Side effects are rare, but when they do occur they are usually mild, although in a few instances it may be necessary to reduce the dosage temporarily.

**Dosage.**—The average oral dose for the treatment of menopausal symptoms is 0.5 to 1 mg. daily by mouth, although if necessary 10 to 25 mg. may be given parenterally biweekly. Dosage for atrophic genital disorders such as kraurosis vulvae include 1 to 5 mg. daily by mouth or 25 mg. weekly by parenteral injection; for the prevention of breast engorgement 5 to 10 mg. daily or 25 mg. the first and third days by injection; for suppression of lactation 10 mg. two or three times daily, or 25 mg. daily by injection; for prostatic cancer 2.5 mg. three times daily by mouth. The duration of treatment varies and may last for several months or even two or three years in the treatment of the menopause, a few months for atrophic genital disorders, three to five days for prevention of breast engorgement and suppression of lactation or be continuous for prostatic cancer.

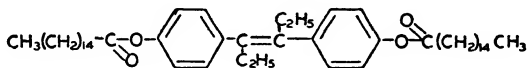
WALLACE & TIERNAN PRODUCTS, INC.

**Solution Monomestrol in Oil:** 10 mg. and 25 mg. per cc., 1 cc. ampuls in sesame oil.

**Tablets Monomestrol:** 0.25 mg., 0.5 mg., 1.0 mg., 2.5 mg. and 5.0 mg.

U. S. patent 2,385,468 (Sept. 25, 1945; expires 1962) and U. S. trademark 397,572.

**STILPALMITATE.**—Diethylstilbestrol *dipalmitate*.—The *dipalmitic acid ester* of diethylstilbestrol.—The structural formula of diethylstilbestrol *dipalmitate* may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses of stilpalmitate are essentially those of diethylstilbestrol except that the absorption of stilpalmitate is slower. This delay in absorption permits a more prolonged therapeutic effect and is believed to lessen unpleasant side effects.

The contraindications for this preparation are the same as those for all substances with estrogenic action.

**Dosage.**—Stilpalmitate is given by intramuscular injection only. The usual dose is 5 mg. in terms of the diethylstilbestrol content. As with other estrogens, individual patient response will vary considerably as to rapidity of symptom relief and duration of effect. In the treatment of menopausal symptoms it is suggested that 5 mg. of diethylstilbestrol as the *dipalmitate ester* be injected every five to seven days for three to five doses, or until the patient obtains satisfactory relief. Treatment is then interrupted until symptoms recur. At that time injections may be repeated at five to seven day intervals until symptoms are again relieved. The duration of symptomatic relief between dosage periods will vary from four to twelve weeks.

Lactation may be suppressed during the puerperium by the injection of 10 mg. of diethylstilbestrol as the *dipalmitate ester* on the day of delivery and 5 mg. on the first and second postpartum days.

Ampuls must be immersed in hot water to dissolve the stilpalmitate, which is insoluble at room temperature. The drug will remain in solution at body temperature.

ABBOTT LABORATORIES

**Solution Stilpalmitate in Oil:** 1 cc. ampuls. Ampuls containing 7 mg. of stilpalmitate per cc. or 14 mg. of stilpalmitate per cc., dissolved in peanut oil.

## Pancreas

The pancreas is a gland having, in general, two functions: (1) It secretes into the intestine a digestive juice containing the enzymes trypsin, lipase and amylase; (2) it secretes into the

blood a hormone, insulin, which regulates the process of carbohydrate metabolism.

When insulin secretion is deficient, or possibly when there is an overproduction of sugar due to other causes, diabetes develops. In this disease the percentage of sugar increases in the blood (hyperglycemia) so that sugar overflows into the urine (glycosuria). The hyperglycemia is associated with a breakdown of the first and last stages in the metabolism of sugar, as revealed, respectively, by failure of glycogen to be deposited in the liver and by failure of the respiratory quotient to become increased when carbohydrate food is ingested. The depression in carbohydrate metabolism may be accompanied by an accumulation of ketone substances (acetone, acetoacetic and oxybutyric acids) with resultant acidosis and, later, coma.

Insulin, if administered subcutaneously, intravenously, or intraperitoneally, causes a fall in the percentage of sugar in the blood. The exact mode of action is not definitely known but experimental evidence suggests that besides increased oxidation of sugar, increased storage as glycogen in the liver and possibly in the muscles is a factor in the result. When the percentage of blood sugar falls below the kidney threshold in the diabetic patient, sugar disappears from the urine. If an overdose of insulin is given, the blood sugar falls to a subnormal level, and characteristic symptoms are observed. The level at which these symptoms occur depends not only on the extent but also on the rate of fall. If the blood sugar has been persistently high and is rapidly reduced, hypoglycemic symptoms may appear at a much higher level of blood sugar than when the fall is slower and more gradual. These symptoms are due to the diminished sugar in the blood, as shown by the fact that they are relieved by the replacement of the sugar by oral or intravenous administration.

Clinical assays conducted on patients with uncomplicated diabetes on certain standard dietary regimens reveal that one insulin unit will on an average promote the metabolism of approximately 1.5 Gm. of dextrose. The physician may, therefore, gauge his insulin dose with some precision. To do so, he must know how much dextrose the patient will derive from his food and metabolism, and how much insulin the patient himself can provide from his insulin-making tissues. The latter may be determined by measuring the patient's ability to utilize carbohydrate without extra insulin. In any case, insulin injections must be made at regular intervals and must be supplemented by accurately weighed diets of known composition.

When properly employed, insulin is a specific in the treatment of diabetic coma and acidosis. It is of pronounced value in the management of diabetic patients undergoing surgery and of those with complicating infectious diseases. It makes possible freedom from glycosuria and good mental and physical vigor for patients with severe diabetes.

There is as yet no positive evidence that treatment with insulin will arrest the diabetic process by restoring the patient's anti-diabetic function. In the severer cases, the evidence now available



is against such an assumption. In the milder cases in which insulin has been used, the evidence is difficult of interpretation because such patients may show very marked improvement in their ability to utilize carbohydrate on dietary regulation and exercise alone.

*Oral Administration of Pancreatic Preparations.*—In diabetes, reliance on the oral administration of the pancreatic preparations thus far available has no justification and such practice merits the most vigorous condemnation. Many reputed anti-diabetic pancreatic preparations are on the market with claims that they are effective if taken by mouth. The most widely heralded of them have been subjected to the scrutiny of clinical tests controlled with simultaneous laboratory investigation. None of these thus tested has shown any effect on blood sugar or glycosuria. Completely negative results were obtained when these preparations were given in the doses recommended by their exploiters as well as in doses twenty times as large. The claim that such preparations exert, in some mysterious manner, a rejuvenating or stimulating action on the diseased pancreas is based on uncontrolled clinical observation.

### Insulin Labeling Regulations

Regulations concerning the certification of batches of drugs composed wholly or partly of insulin are presented in the 8 Federal Register 11837, Aug. 27, 1943. Of special interest to the physician are statements on labeling. Each package must contain on the outside wrapper information on the batch mark, strength of the drug in terms of U. S. P. units of insulin per cc., expiration date, and the warning "Keep in a cold place: Avoid freezing." The circular or other labeling must contain special information for the guidance of the physician. The outside containers or wrappers must be distinguished by various colors.

**Insulin U. S. P. is distinguished by:**

*Yellow*, if it contains 20 U. S. P. Units of insulin per cubic centimeter.

*Red*, if it contains 40 U. S. P. Units of insulin per cubic centimeter.

*Green*, if it contains 80 U. S. P. Units of insulin per cubic centimeter.

*Orange*, if it contains 100 U. S. P. Units of insulin per cubic centimeter.

If the master lot used was in crystalline form the distinguishing colors may be:

*Blue* and *gray*, or *blue*, *gray* and *yellow*, if it contains 20 U. S. P. Units of insulin per cubic centimeter.

*Red* and *gray*, if it contains 40 U. S. P. Units of insulin per cubic centimeter.

*Green* and *gray*, if it contains 80 U. S. P. Units of insulin per cubic centimeter.

**Protamine zinc insulin is distinguished by:**

*Red* and *white*, if it contains 40 U. S. P. Units of insulin per cubic centimeter.

*Green* and *white*, if it contains 80 U. S. P. Units of insulin per cubic centimeter.

**Globin insulin with zinc is distinguished by:**

*Red* and *brown*, if it contains 40 U. S. P. Units of insulin per cubic centimeter.

*Green* and *brown*, if it contains 80 U. S. P. Units of insulin per cubic centimeter.

**GLOBIN INSULIN WITH ZINC.**—"Globin insulin (with zinc) is a preparation, in a hydrochloric acid medium, of insulin modified by the addition of globin (derived from the hemoglobin of beef blood) and zinc chloride. The quantity of insulin used is such that each cubic centimeter of the finished product contains either 40 or 80 U. S. P. units of insulin. The quantity of globin used (calculated as 6.0 times its nitrogen content) is not less than 3.6 mg. and not more than 4.0 mg. for each 100 U. S. P. units of insulin used. The preparation also contains, for each 100 U. S. P. units of insulin used, not less than 0.25 mg. and not more than 0.35 mg. zinc and not more than 1.50 mg. total nitrogen. The *pH* of the finished preparation is not less than 3.4 and not more than 3.8. If necessary, either hydrochloric acid or sodium hydroxide may be added to obtain the required *pH*. The finished preparation also contains not less than 1.30 and not more than 1.70 per cent (W/V) of glycerin and not less than 0.15 per cent and not more than 0.20 per cent (W/V) cresol-U. S. P., or not less than 0.20 per cent and not more than 0.26 per cent (W/V) phenol-U. S. P. The preparation is sterile."—Regulations promulgated Aug. 24, 1943 by the Administrator, Federal Security Agency: Certification of Batches of Drugs Composed Wholly or Partially of Insulin [8 Fed. Reg. 11837 (Aug. 27, 1943)], as amended [10 Fed. Reg. 2904-2905 (Mar. 17, 1945)].

Standards for Globin Insulin with Zinc and the Globin used in its preparation are set forth in the regulations cited.

**Actions and Uses.**—The effects of globin insulin with zinc are essentially the same as those of insulin (which see) except that the action is intermediate between that following regular insulin and protamine zinc insulin. The period of greatest effect extends from the eighth to the sixteenth hour after injection, almost disappearing at the end of twenty-four hours. This agent may be used for the treatment of diabetic patients in whom regulation of diet alone is incapable of providing adequate control and may be used in some patients to replace, wholly or partly, ordinary insulin. It is claimed to be indicated for those patients

who require more than one daily injection of unmodified insulin and for those who cannot be controlled by other forms of insulin or who exhibit a sensitivity to protamine. It is said also to produce fewer local reactions on injection. It is not recommended for the treatment of diabetic coma and should never be administered intravenously. Globin insulin with zinc is quite stable but nevertheless bears on the label an expiration date for usage.

**Dosage.**—The general principles underlying the administration of this form of insulin are the same as those governing the use of unmodified insulin. It must be administered only by deep subcutaneous injection, not intramuscularly or intravenously. The daily dose required must be determined by a study of the patient. However, a starting dose may be about two thirds to three fourths of the total daily dose of regular insulin. This may be increased slowly as needed. If the patient has been receiving protamine zinc insulin, the globin insulin dosage on the first day should not exceed one-half the total dose of all insulin (regular, protamine zinc) received on the previous day. On the next day the dose may be increased to two thirds of the previous total insulin dosage and then slowly adjusted as required.

BURROUGHS WELLCOME & Co., INC.

**Globin Insulin with Zinc:** 40 and 80 units, 10 cc. vials. Each cc. contains 40 and 80 units of globin insulin with zinc. Contains cresol 0.18 per cent as a preservative.

U. S. patent 2,161,198 (June 6, 1939; expires 1956).

E. R. SQUIBB & SONS

**Globin Insulin with Zinc:** 40 and 80 units, 10 cc. vials. Each cc. contains 40 and 80 units of globin insulin with zinc respectively. Contains phenol 0.25 per cent as a preservative.

**INSULIN INJECTION—U. S. P.—Iletin-Lilly.**—Insulin.—Insulin Hydrochloride.—“An acidified solution of the active principle of the pancreas which affects the metabolism of glucose. Insulin Injection, when assayed as directed, shall possess a potency of not less than 95 per cent and not more than 105 per cent of the potency stated on the label, and the potency shall be expressed in U. S. P. Insulin Units which are equivalent in potency to the Unit declared on the label of the container of the U. S. P. Zinc-Insulin Crystals Reference Standard.

“Insulin Injection is so standardized that each cc. contains either 20, 40, 80, or 100 U. S. P. Insulin Units.”—U. S. P.

For description and standards see the U. S. Pharmacopeia under Insulin Injection.

**Actions and Uses.**—Insulin lowers the blood sugar in normal rabbits causing characteristic symptoms when a low level is reached, which symptoms are overcome by the administration of dextrose. It prevents the hyperglycemia due to piqure,

asphyxia and epinephrine. It increases the sugar consumption of the isolated mammalian heart. It causes glycogen to be deposited in the liver of diabetic animals fed with carbohydrates, and raises the respiratory quotient of such animals. It affects the metabolism of fat in diabetic animals and causes the acetone bodies to disappear from the urine. It has been demonstrated that the administration of insulin to diabetic dogs and to man in severe cases of diabetes mellitus restores temporarily to the body the impaired ability to oxidize carbohydrate, and that glycogen is again stored in the liver. If a suitable dose of insulin is administered at suitable intervals to a person suffering from diabetes mellitus, the blood sugar is maintained at a normal level and the urine remains free of sugar; fat is also burned and as a result, ketone bodies do not appear in the urine and diabetic acidosis and coma are prevented.

The administration of insulin is indicated in cases of diabetes mellitus which cannot be controlled at a satisfactory level by dietetic treatment. In such cases, with proper regulation of the diet, insulin should be administered in such amounts as to prevent glycosuria and a too great hyperglycemia. In some cases the dosage of insulin may be gradually decreased as the body power of utilizing carbohydrate returns toward normal.

Overdosage of insulin is followed by the development of serious symptoms which demand immediate treatment. The patient complains of weakness and fatigue and a feeling of nervousness or tremulousness. This is followed by profuse sweating, which is the most characteristic sign of overdosage. There is sometimes pallor or flushing. In the more severe forms there is acute distress with mental disturbances and even unconsciousness. These symptoms are relieved by the administration of some form of soluble carbohydrate, such as orange juice, by mouth or stomach tube, or, if the patient is comatose, by the intravenous injection of from 5 to 20 grams of pure dextrose in a 5 to 50 per cent sterile solution. Although symptoms of hypoglycemia usually develop gradually, the onset in occasional cases may be sudden. In view of this, ambulant patients should be instructed to carry, for immediate use, soluble carbohydrate in the form of powdered dextrose or an orange. Physicians treating patients with insulin should be impressed with the necessity of having adequate supplies of sterile solution of dextrose at hand. In case of emergency when sterile solution of dextrose is not available, a subcutaneous injection of 0.3 cc. to 0.6 cc. of 1 in 1,000 solution of epinephrine may be employed, but this must always be followed by carbohydrates by mouth. The injection of epinephrine must be employed carefully as its action depends on the presence of glycogen, of which there is usually very little in the diabetic organism. Epinephrine should never be employed when the hypoglycemia follows excessive exercise, vomiting or the omission of meals.

Insulin has been used in the treatment of non-diabetic malnutrition with reported increase in appetite and gain in weight. Care is necessary in avoiding symptoms of hypoglycemia.

Insulin has been suggested and used rather extensively in psychopathic hospitals for the purpose of producing hypoglycemic shock for its effect on the schizophrenic. It is a dangerous procedure with a relatively high mortality and should be employed only by those who are fully equipped, fully qualified and thoroughly familiar with all aspects of this method of treatment. Obviously it is essential to have available at all times suitable solutions of dextrose for interrupting the hypoglycemic state which is artificially created in these individuals by the administration of insulin.

*Dosage.*—Insulin is administered by injection into the loose subcutaneous tissue of the body, usually thirty minutes before meals. There is no average dose of insulin for diabetics; each case must be studied individually. Except when complications occur insulin is not indicated when a patient has adequate dextrose tolerance to provide him with a diet sufficient for light work. The dose depends upon the amount of dextrose in such a diet as he is unable to metabolize; i.e., the total dextrose minus the dextrose excretion. A convenient formula is: Average grams of d-glucose excreted

1.5

= sufficient units of insulin to render most patients aglycosuric. Usually the daily dose is administered in two equal portions, one before breakfast and the other before supper. The carbohydrate of the diet should be distributed between the three meals. With large daily dosage (40 units or more) insulin may be injected before each meal; less carbohydrate should be given at breakfast than at the other two meals. When the patient becomes aglycosuric the diet can usually be increased. Sufficient insulin should be used to keep the fasting blood sugar normal, but hypoglycemia should be avoided. If patients are not under close observation, half the estimated dose may be used and the dose gradually increased until therapeutic results are obtained. Complications, such as infections, may reduce the dextrose tolerance, thus necessitating an increase of insulin dosage.

In cases of coma or severe acidosis an initial dose of 30-60 units may be given (in coma one-half the amount intravenously and one-half subcutaneously) followed at  $\frac{1}{2}$  to 3 hour intervals by doses of 20 units or more subcutaneously. Some physicians administer 1 Gm. of dextrose for each unit of insulin used. The patient should never become hypoglycemic. Examine the urine hourly for dextrose. If urine becomes sugar free more dextrose must be given. More than 150 units of insulin in twelve hours is rarely needed. Young children with diabetes of recent onset usually require smaller doses and seldom more than 80 units in the first 12 hours.

In a small number of cases of diabetes mellitus, insulin can be discontinued, particularly with patients who receive it because of an exacerbation caused by complications, and where diabetes is of recent onset (though perhaps the latter should receive it intermittently as a prophylactic against increasing severity).

*Dosage of insulin should always be expressed in units rather than in cubic centimeters or minims.* The volume of a dose of insulin containing a certain number of units will vary with the strength of the solution which is employed. In general it is advisable to keep the volume per injection at from  $\frac{1}{4}$  to  $\frac{3}{4}$  cc., choosing the strength of insulin which will give the required number of units in this volume or less.

U. S. patents 1,469,994 (Oct. 9, 1923; expired); 1,470,024 (Oct. 9, 1923; expired) and 1,520,673 (Dec. 23, 1924; expired). Canadian patent 234,336 and 234,337. U. S. trademark 179,174. Canadian trademark 31,646.

#### ELI LILLY AND COMPANY

**Iletin:** U-40 and U-80, 10 cc. vials. Each cc. contains 40 and 80 units insulin respectively.

U. S. trademark 171,971.

#### SHARP & DOHME, INC.

**Insulin:** 40 units, 80 units, 100 units, 10 cc. vials. Each cc. contains 40, 80 and 100 units respectively.

Beef pancreas is rendered as free from fat and connective tissue as possible, and extracted with acidulated 60 per cent alcohol. The mixture is centrifugized and the gland residue reextracted with 60 per cent alcohol. The alcoholic liquid is then concentrated to about one twelfth its original volume. The active substance is then precipitated with ammonium sulfate, and reprecipitated from an alcoholic solution. It is further purified by a method of iso-electric precipitation and is finally dissolved in acid water (pH 2.5). 0.25 per cent phenol is used as preservative and glycerin 1.6 per cent is added in order to attain isotonicity. It is then filtered through a Berkefeld filter and submitted to sterility tests; its potency is determined by the method described under the preceding article, Insulin.

#### E. R. SQUIBB & SONS

**Insulin:** 40 units, 80 units, 100 units, 10 cc. vials. Each cc. contains 20, 40, 80 and 100 units respectively.

Insulin Squibb is made by extracting finely ground beef pancreas with acidulated aqueous alcohol and subsequently removing the tissue by centrifuging. The alcoholic solution is concentrated and the insulin is precipitated by ammonium sulfate after the removal of fats. This sulfate precipitate is dissolved in dilute ammonia and impurities removed by alcoholic precipitation. From the above filtrate the insulin is precipitated with ether and redissolved in ammonia. It is then reprecipitated at its iso-electric point pH 4.8-5.2. This nearly pure insulin precipitate is centrifuged and dissolved in acid water which is then passed through a Berkefeld filter and assayed. The finished preparation contains 0.1 per cent phenol as a preservative.

Fresh pancreatic glands of animals, from which fat and connective tissue have been removed, are ground and extracted with  $1\frac{1}{2}$  volumes 95 per cent alcohol, containing 0.11 per cent absolute sulfuric acid. The mixture is agitated during two hours and then filtered. The residue is again extracted using an equal volume of 70 per cent alcohol containing 0.11 per cent absolute sulfuric acid. This is filtered and the filtrate added to the first filtrate. The combined filtrates are chilled to 0 C. and filtered. The filtrate is concentrated to about one twenty-fifth its original volume and filtered, and the filtrate added to 5.3 times its volume of 95 per cent alcohol. This mixture is allowed to stand for several hours, and then filtered, and the filtrate made up to contain 93 per cent alcohol. After standing several days, the precipitate formed is collected and dissolved in distilled water. The insulin preparation is further purified by precipitation at the isoelectric point, the hydrogen ion concentration

being adjusted to approximately pH 4.7, after which the solution is allowed to stand in the icebox. The precipitate formed is dissolved in acidified water (pH 2.5), filtered, reprecipitated and redissolved if necessary for further purification. The solution is then diluted to approximately the desired potency, filtered through a Berkefeld filter, and submitted to standardization and sterility tests. The finished preparation contains 0.2 per cent phenol as a preservative.

### PROTAMINE ZINC-INSULIN INJECTION- U. S. P.

—Protamine, Zinc and Iletin-Lilly.—“A suspension, in a buffered water medium, of insulin modified by the addition of zinc chloride and protamine. The protamine is prepared from the sperm or from the mature testes of fish belonging to the genera *Oncorhynchus* Suckley, *Salmo* Linné, or *Trutta*, Jordan and Evermann (Fam. *Salmonidae*), and conforms to the regulations of the Food and Drug Administration concerning certification of batches of drugs composed wholly or partly of insulin.

“In the preparation of Protamine Zinc Insulin Injection the amount of insulin used is sufficient to provide either 40 or 80 U. S. P. Insulin Units for each cc. of the Injection.

“*Note—Protamine Zinc Insulin Injection differs in its action from that of Insulin Injection . . . both in time of onset and duration. To secure accuracy of dosage the preparation must be brought into uniform suspension by careful shaking before use.*”  
U. S. P.

For description and standards see the U. S. Pharmacopeia under Protamine Zinc-Insulin Injection.

**Actions and Uses.**—The effects of protamine zinc insulin are the same as those of Insulin (which see), except that the blood-sugar-lowering action of unmodified insulin becomes maximal in from two to three hours, whereas the blood-sugar-lowering action of protamine zinc insulin is prolonged and has its greatest effect in about twelve to twenty-four hours after administration.

Protamine zinc insulin may be used in the case of any patient where regulation of diet is incapable of removing the cardinal objective symptoms of diabetes mellitus, and may replace, wholly or partly, the use of unmodified insulin in the treatment of the patient. In some cases the use of unmodified insulin alone is desirable; in others, protamine zinc insulin alone is indicated; while in others, the use of both preparations gives best results.

In view of the prolonged action of protamine zinc insulin, the chief indications for its use are in those cases where unmodified insulin is unable to provide control, without being administered in several doses daily, or is unable to provide adequate control unaccompanied by frequent hypoglycemic reactions, ketosis, or evidence of pronounced fluctuations in blood sugar levels. The usefulness of protamine zinc insulin in cases of diabetic coma, in diabetes complicated by infection, or in the event of surgical operations has not been definitely established. In such instances, therefore, the use of protamine zinc insulin to supplant the use of unmodified insulin is not recommended.

**Dosage.**—The general principles underlying the administration

of protamine zinc insulin are the same as those governing the administration of unmodified insulin (see Insulin Injection).

Protamine zinc insulin is to be injected *only subcutaneously*. In most cases its administration more often than once a day is not required. The initial dose should be from about two-thirds to equal the number of units that would be needed daily to maintain the patient "sugar free" under treatment with unmodified insulin. In some instances glycosuria may follow owing to the slow absorption and consequent delayed action of protamine zinc insulin. Hence on the first few days when protamine zinc insulin is being used, it may be advantageous to administer a separate dose of unmodified insulin. It is usually possible to discontinue the use of unmodified insulin after the first or second day, though in some instances the administration of both preparations requires to be continued indefinitely.

Protamine zinc insulin is generally administered either in the morning (from one-half to one and one-half hours before breakfast), or in the evening (one hour before supper or one hour before retiring). Diet must be adjusted with the prolonged blood-sugar-lowering effect of the product in mind, and a redistribution of food among individual meals is usually desirable. In particular, the carbohydrate content of the meal following the injection of protamine zinc insulin may have to be limited in order to avoid *hyperglycemia*. The carbohydrate of the diet not included in this meal is divided between the other meals of the day in such a manner as to prevent *hypoglycemia* at times when the dose of protamine zinc insulin is exerting its greatest effect.

Symptoms of hypoglycemic reactions following administration of protamine zinc insulin are similar to but may be less obvious than those following injection of unmodified insulin, and may consist merely of a feeling of pronounced fatigue unwarranted by the activities of the patient. When a hypoglycemic reaction is occasioned by protamine zinc insulin, the reaction may be prolonged, and despite its having been treated, it may repeat itself owing to the continuing effect of the dose administered. It is therefore advisable to use both a soluble and a more slowly digestible carbohydrate in treating such reactions, for example, corn syrup with bread or bread with honey. Alternatively, and even though the patient may *appear* to be restored to normal through use of a soluble carbohydrate food such as orange juice, it is advisable to provide additional carbohydrate after the lapse of one or two hours. Soda biscuits and milk are suitable at that time. In severe reactions, it may be desirable to inject from 15 to 20 Gm. of dextrose in sterile solution intravenously, followed later by food.

#### ELI LILLY AND COMPANY

**Protamine Zinc and Iletin:** 40 units and 80 units, 10 cc. vials. Each cc. contains 40 and 80 units of protamine zinc insulin respectively.

Iletin is registered under U. S. trademark 171,971.



SHARP & DOHME, INC.

**Protamine Zinc Insulin:** 40 units and 80 units, 10 cc. vials. Each cc. contains 40 and 80 units of protamine zinc insulin respectively. Contains disodium acid phosphate 0.2 per cent, phenol 0.25 per cent as a preservative, and glycerin 1.6 per cent for isotonicity.

E. R. SQUIBB & SONS

**Protamine Zinc Insulin:** 40 units and 80 units, 10 cc. vials. Each cc. contains 40 and 80 units of protamine zinc insulin respectively.

**ZINC INSULIN CRYSTALS.**—Zinc insulin crystals are a crystalline preparation of the active antidiabetic principle of the internal secretion of the islands of Langerhans of the pancreas. The crystals contain a small amount of zinc (not less than 0.45 per cent and not more than 0.9 per cent), which is chemically combined with the active principle. Each milligram of the crystals is equivalent to not less than 22 units of insulin. The product is marketed in the form of crystalline zinc-insulin injection.

For tests and standards, see Section B.

**CRYSTALLINE ZINC INSULIN INJECTION.**—**Insulin Made from Zinc Insulin Crystals.**—A solution of zinc insulin crystals, a preparation containing the active antidiabetic principle of the pancreas, combined with a small amount of zinc (not less than 0.2 and not more than 0.40 mg. per thousand units of active principle in the solution).

Crystalline zinc insulin injection meets the requirements for identity and purity provided in the U. S. P. under Insulin Injection.

*Actions and Uses.*—Crystalline zinc insulin injection may be used in the treatment of diabetes mellitus when regulation of diet has been unsatisfactory in control of the disease. Because of its chemical purity, solution of zinc insulin crystals is especially indicated for patients who may be expected to exhibit allergic reactions to insulin. Experience has indicated that the occurrence of such reactions may thus be avoided or minimized. Although early clinical observations indicated that the action of crystalline zinc insulin injection as compared with that of insulin may be slightly delayed and somewhat prolonged, further clinical experience has shown that, in patients under careful observation, crystalline zinc insulin injection and insulin may be used interchangeably.

*Dosage.*—The potency of crystalline zinc insulin injection is measured in terms of standard units of insulin. The general principles underlying its administration are the same as those covering the use of insulin, and under ordinary circumstances the two solutions may be regarded as interchangeable. The

crystalline zinc insulin injection is usually best administered subcutaneously fifteen to thirty minutes before a meal. The time and number of the doses and the amount of solution must be determined by the need of the individual patient, each of whom requires accurate dietary regulation and meticulous clinical study.

Marketed solutions of zinc insulin crystals are water clear and contain from 1.4 to 1.8 per cent W/V of glycerin for isotonicity; 0.1 to 0.25 per cent W/V of phenol or tricresol as a preservative and sufficient 0.01 normal hydrochloric acid to yield a  $\rho\text{H}$  of from 2.5 to 3.5. The biologic activity of the solution is expressed in U. S. P. insulin units per cubic centimeter. Solutions of zinc insulin crystals are stable, provided the storage temperature does not exceed room temperature.

### Parathyroid

Parathyroid preparations for oral administration are made from the dried gland and for subcutaneous administration by extraction of the gland by suitable solvents and subsequent purification of the product. The reports of success after oral therapy lack any conclusive evidence that this was dependent upon the use of the gland. No proof has been brought forward that the one definite effect that can be referred to the parathyroid gland (maintaining or raising the calcium concentration of the serum) has been produced by parathyroid preparations taken by mouth. To ascribe to the oral administration of parathyroid preparations improvement in conditions that are not definitely known to depend upon parathyroid disease, or deficiency, is illogical and misleading. In consideration of the accumulated evidence of the ineffectiveness of oral therapy with parathyroid, preparations of parathyroid designed for oral administration are not accepted for inclusion in this book.

Preparations which have a powerful influence on calcium metabolism may be made from the parathyroids of the ox. If this substance is injected intramuscularly or subcutaneously, the calcium concentration of the serum of animals deprived of their parathyroid glands can be raised and maintained at a normal limit. By repeated doses it may be raised far beyond this, either in parathyroidectomized or in normal animals and unless the dosage is carefully regulated, death may ensue. The preparations can be standardized according to their activity in raising the calcium concentration in parathyroidectomized animals or in normal animals. On subcutaneous and intramuscular injections the plasma calcium begins to rise in about 4 hours, reaches its maximum in from 12 to 18 hours and returns to the previous level in from 20 to 24 hours. Associated with the rise in serum calcium is an increased urinary excretion of calcium and inorganic phosphate and a decrease in the serum content of the latter. An immunity or tolerance to the hormone is induced by repeated administration. Treatment by these parathyroid preparations has been shown to be of value in tetania parathyreopriva. In infantile tetany their employment should be confined to those

cases in which a reduction in the level of serum calcium has been demonstrated and would appear to be a temporary expedient until other measures have an opportunity to combat the fundamental underlying condition. In gastric tetany the calcium of the serum is normal, and it has not been demonstrated that this condition can be affected beneficially by parathyroid therapy. The available clinical or scientific evidence does not permit an estimate of the ultimate usefulness of the parathyroid preparation in other conditions. The danger of hypercalcemia, which is easily induced by overdosage and which is associated with grave manifestations, makes it desirable that the clinical use of parathyroid preparations should be controlled by blood serum calcium determinations or by application of the Sulkowitch test for calcium in the urine. The normal concentration of calcium in human serum being approximately 10 mgm. of calcium per 100 cc. of serum, values above 12 mgm. are considered undesirable while those above 15 mgm. may be dangerous. Injections of parathyroid solutions may produce troublesome local reactions, which interfere with their continued use. Repeated doses may establish tolerance to the hormone, with almost complete loss of therapeutic effect. For this reason, other substances, such as dihydrotachysterol or calciferol, which cause elevation of serum calcium, should be substituted as soon as possible.

**PARATHYROID INJECTION-U. S. P.—Paroidin-Parke, Davis.**—Parathyroid Extract.—Parathyroid Solution.—“A sterile solution in water for injection of the water-soluble principle or principles of the parathyroid glands which have the property of relieving the symptoms of parathyroid tetany and of increasing the calcium content of the blood serum in man and other animals. It is obtained from the fresh parathyroid glands of healthy domesticated animals used for food by man, the animal source of each preparation being stated. The parathyroid glands must be removed from the animals immediately after slaughtering, and then extracted at once or kept frozen until extracted. The glands are freed from gross fat and connective tissue, ground, extracted, and the extract purified to make it suitable for parenteral administration. The injection is then adjusted to the proper potency.

“One cc. of Parathyroid Injection possesses a potency of not less than 100 U. S. P. parathyroid units, each unit representing one one-hundredth of the amount required to raise the calcium content of 100 cc. of the blood serum of normal dogs 1 mg. within 16 to 18 hours after administration.” *U. S. P.*

For description and standards see the U. S. Pharmacopeia under Parathyroid Injection.

*Actions and Uses* (See general article, Parathyroid).

*Dosage.*—In severe seizures of acute proved parathyroid tetany such as may follow removal of the parathyroid glands during thyroidectomy a dose of 100-300 units (1.0-3.0 cc.) may be necessary. Beneficial effect, as evidenced by an elevation in the

serum calcium, is usually apparent within a few hours and reaches a maximum in 8-18 hours. For maintenance of the level of serum calcium the average adult dose is 0.2-0.4 cc. (20-40 units) every 12 hours. The continuance and regulation of such dosage must be controlled by determinations of the level of the serum calcium. In the treatment of chronic parathyroid tetany parathyroid injection is less effective than dihydrotachysterol or vitamin D<sub>2</sub> and is usually unnecessary if one of these substances can be provided in appropriate amounts. In infants the use of parathyroid injection should be more cautious and even in those cases where a reduction of serum calcium has been demonstrated the initial dosage should not exceed 0.1-0.2 cc. (10-20 units).

#### ELI LILLY AND COMPANY

**Solution Parathyroid Extract:** 1 cc. ampuls and 5 cc. vials. Each cc. contains 100 units.

#### PARKE, DAVIS & COMPANY

**Solution Paroidin:** 5 cc. vials. Each cc. contains 100 units. U. S. patent 1,890,851 (Dec. 13, 1932; expires 1949). U. S. trademark.

### Pituitary

*Posterior Lobe.*—The posterior lobe of the pituitary gland yields on extraction substances having a marked effect on smooth muscle, especially that of the blood vessels and the uterus. The intravenous or intramuscular injection of preparations of the posterior lobe is sometimes followed by an increase in blood pressure which is maintained over a considerable period of time. Injection of subsequent doses in such cases is followed by a similar effect unless repeated too soon after the first injection, when a fall in pressure may occur. The increase in pressure is due to an action on the smooth muscle of the vessels. In a considerable number of individuals the increase in blood pressure may be very slight and in some instances instead of an increase a definite lowering of the blood pressure may follow the injection of pituitary preparations. The heart is not stimulated in any case and may be depressed, either through the vagus response to a high blood pressure or by a direct action on the heart muscle itself or through impairment of its nutrition because of constriction of the coronary vessels. The tone of the intestinal tract may be markedly increased by direct action on the muscular coat. The administration of extracts usually retards the secretion of urine to a marked degree during the first hour and a half and sometimes longer. There is some experimental evidence to show that the absorption of water from the gastrointestinal tract is delayed, thereby lessening the water available for secretion. However, the antidiuretic action may be due to increased reabsorption of water from the kidney tubules into the blood. The bladder musculature is stimulated especially when it has been previously in an atonic condition. Posterior

pituitary extract does not increase the formation of milk, but may cause a temporary acceleration of the output. The extract of the posterior lobe causes a marked contraction of the uterus by a direct stimulating action on the muscle. The intensity of the action varies with the species animal, the stage in the estrus or menstrual cycle, the presence or absence of pregnancy and the stage of pregnancy.

Solutions prepared from the posterior lobe injected intramuscularly are employed against uterine atony and in postpartum as well as in other forms of uterine hemorrhage. They should not be injected during the first stage of labor because, if the cervix be not fully dilated, energetic contractions may cause rupture of the uterus or extensive laceration of the soft tissue. Most authorities also advise against the use of pituitary preparations in the second stage of labor.

Pituitary solutions may be useful in intestinal paresis whether following abdominal operations or complicating infectious diseases. The extracts are also extensively used in diabetes insipidus, in which they reduce greatly the volume of urine excreted. For this purpose they are injected once or twice daily. The extracts should always be injected hypodermically or intramuscularly although some activity appears when they are applied to the nasal mucous membrane. The extract of the posterior lobe of the pituitary gland has been fractionated: one product (Pitocin) acting on the uterus and a second product (Pitressin) acting on the blood vessels, intestine and urinary secretion. Pitressin also has an oxytocic action on the human uterus but its other effects make it less desirable as an oxytocic agent.

*Anterior Lobe.*—Hyperactivity of the anterior lobe is believed to produce gigantism and acromegaly, for clinically both conditions have been accompanied by tumors of the pituitary. Evidence has accumulated which indicates that the hormones of the anterior lobe are essential to normal growth and the development of the ovaries and testes, but that they may have nothing to do with some of the other disturbances formerly attributed to abnormal functioning of the pituitary, as a considerable number of cases of adiposogenital dystrophy have come to autopsy in which the pituitary has been histologically normal. It is also claimed that extirpation of the hypophysis in adult dogs and white rats without injury to the hypothalamus does not produce dystrophia adiposogenitalis. Extirpation in immature animals is followed by cessation of growth and sexual development, a condition which has been corrected in white rats by daily transplants of the anterior lobe of the pituitary or by daily injections of appropriate amounts of the fresh extract of the anterior lobe of bovine glands.

Present evidence would seem to indicate that a number of factors are concerned in the action of extracts of the anterior lobe: (1) a growth factor concerned with the development of the body; (2) a factor which stimulates the growth and matu-

ration of the ovarian follicle, which in turn bring on the changes characteristic of estrus; (3) a factor which causes luteinization of the ovarian follicles; (4) a factor which is necessary for normal thyroid development and function and which, if present in excess, produces hyperplasia of the thyroid with hyperthyroidism in both the rat and the guinea pig; (5) a factor which produces lactation in mammals, and possibly plays a part in mammary gland proliferation; it also induces a secretion of crop milk in pigeons; (6) a diabetogenic principle which decreases the hypoglycemic response to insulin and which has been shown experimentally to damage indirectly the cells of the islets of Langerhans thus producing the diabetic syndrome; and (7) a ketogenic principle, apparently distinct from the diabetogenic factor, which increases the ketone content of the blood in rabbits and rats. In addition to the above enumerated factors, the existence of which seems to be clearly established, experimental evidence has been offered indicating the presence of other principles; among these is one which stimulates the adrenal cortex known as the adrenotropic hormone. This has recently been prepared in relatively pure form.

The Council believes that extensive clinical trial has failed to establish the value of desiccated pituitary preparations for oral administration whether these are prepared from the anterior or from the posterior lobe.

**ALPHA-HYPOPHAMINE.**—*Pitocin-Parke, Davis.*—An aqueous solution containing the oxytocic principle of the posterior lobe of the pituitary gland (alphahypophamine) containing less than  $\frac{1}{2}$  unit of pressor activity per cubic centimeter. Five-tenths per cent of chlorbutanol is used as a preservative. It is standardized by the U. S. P. method for posterior pituitary, each cubic centimeter containing 10 units. *Alpha*-hypophamine therefore has an activity on the uterus equal to that of the U. S. P. solution of pituitary.

*Actions and Uses.*—*Alpha*-hypophamine is used to stimulate uterine contractions in obstetrical practice and to stop post-operative bleeding.

The use of the product may be particularly indicated in those cases in which increase of blood pressure is undesirable. Its use is contraindicated in contracted pelvis and in incomplete dilatation of the cervix. (See general article, Pituitary.)

*Dosage.*—From 0.3 cc. to 1 cc. intramuscularly. If used before delivery is completed, small doses are used, repeated if necessary in twenty to thirty minutes.

PARKE, DAVIS & COMPANY

**Solution Pitocin:** 0.5 cc. and 1 cc. ampuls.

U. S. patent 1,960,493 (May 29, 1934; expires 1951). U. S. trademark 254,956.

**BETA-HYPOPHAMINE.**—**Pitressin-Parke, Davis.**—An aqueous solution containing the pressor and diuretic-antidiuretic principle of the posterior lobe of the pituitary gland, (betahypophamine) containing less than 1 unit of oxytocic activity per cubic centimeter. Five-tenths per cent of chlorbutanol is used as a preservative. It is standardized by the method of Hamilton and Rowe (*J. Lab. & Clin. Med.* 2: 120 [Nov.] 1916) so that each cubic centimeter contains 20 pressor units (1 unit represents the pressor activity exhibited by 0.5 mg. of Posterior Pituitary U. S. P. Reference Standard-U. S. P.). It has, therefore, twice the pressor potency of Posterior Pituitary Injection U. S. P.

*Actions and Uses.*—*Beta*-hypophamine is used for raising the blood pressure, for increasing the muscular activity of the bladder and intestinal tract, also for antidiuretic effect in diabetes insipidus. (See preceding article, Pituitary.)

Experimental evidence has been obtained indicating that the product increases the blood sugar and it has been successfully employed to counteract overdoses of insulin in animals. No clinical studies to determine the value for this purpose have been reported so far. It has been suggested that the product may be of value either in conjunction with or supplementary to the use of epinephrine in the treatment of serum sickness and similar vasomotor disturbances, but no definite evidence on this point is as yet available.

*Dosage.*—From 0.3 to 1 cc. intramuscularly, repeated as may be indicated.

PARKE, DAVIS & COMPANY

**Solution Pitressin:** 0.5 cc. and 1 cc. ampuls.

U. S. patent, 1,960,493 (May 29, 1934; expires 1951). U. S. trademark 254,507.

**BETA-HYPOPHAMINE TANNATE.**—**Pitressin Tannate in Oil-Parke, Davis.**—A suspension in vegetable oil of a water insoluble tannate of the pressor and diuretic-antidiuretic principle of the posterior lobe of the pituitary gland (*beta*-hypophamine) standardized to contain five pressor units in each cc. (one unit representing the pressor activity exhibited by 0.5 mg. of standard powdered pituitary U. S. P.). It is standardized by the method of Hamilton and Rowe (*J. Lab. & Clin. Med.* 2: 120 [Nov.] 1916).

*Actions and Uses.*—*Beta*-hypophamine tannate is recommended for use where the prolonged action of *beta*-hypophamine is desired, particularly for the treatment of patients suffering from diabetes insipidus.

*Dosage.*—From 0.3 to 1 cc. (3 to 5 pressor units) intramuscularly, *never intravenously*, at intervals of from 36 to 48 hours.

PARKE, DAVIS & COMPANY

**Solution Pitressin Tannate in Oil:** 1 cc. ampuls. Each cc. contains *beta*-hypophamine tannate equivalent to 5 pressor units, in peanut oil suspension.

U. S. patent 1,960,493 (May 29, 1934; expires 1951). U. S. trademark 254,507.

**POSTERIOR PITUITARY INJECTION-U. S. P.—Pituitrin-Parke, Davis.**—Posterior Pituitary Solution.—“A sterile solution in water for injection of the water-soluble principle or principles from the fresh posterior lobe of the pituitary body of healthy domesticated animals used for food by man. The pituitary body must have been removed from the animal immediately after slaughtering, and then dried or extracted at once or kept frozen until extracted. *The potency of Posterior Pituitary Injection shall be such that 0.1 cc. of the Injection shall possess an activity equivalent to one U. S. P. Posterior Pituitary Unit.*” U. S. P.

For description and standards see the U. S. Pharmacopeia under Posterior Pituitary Injection.

*Actions and Uses.*—See general article, Pituitary.

*Dosage.*—For use in obstetrical cases, from 0.2 to 1 cc.; in surgical cases, from 1 to 2 cc., preferably by deep intramuscular injection or subcutaneously.

ABBOTT LABORATORIES

**Solution Posterior Pituitary:** 0.5 cc. and 1 cc. ampuls.

THE ARMOUR LABORATORIES

**Solution Posterior Pituitary:** 0.5 cc. and 1.0 cc. ampuls. Preserved with 0.5 per cent chlorobutanol.

ENDO PRODUCTS, INC.

**Solution Posterior Pituitary:** 0.5 cc. and 1 cc. ampuls. Preserved with 0.25 per cent chlorobutanol.

THE HARROWER LABORATORY, INC.

**Solution Posterior Pituitary:** 1 cc. ampuls and 10 cc. vials. Chlorobutanol, 0.5 per cent as a preservative.

LAKESIDE LABORATORIES, INC.

**Solution Posterior Pituitary:** 1 cc. ampuls, 10 cc. and 30 cc. vials.

ELI LILLY AND COMPANY

**Solution Posterior Pituitary:** 0.5 cc. and 1 cc. ampuls. Preserved with 0.2 per cent phenol.

THE WM. S. MERRELL COMPANY, LOESER LABORATORY DIVISION

**Solution Posterior Pituitary:** Preserved with 0.5 per cent chlorobutanol.



**PARKE, DAVIS & COMPANY**

**Solution Pituitrin:** 0.5 cc. and 1 cc. ampuls. Preserved with 0.5 per cent chlorobutanol.

U. S. trademark 76,722.

**E. R. SQUIBB & SONS**

**Solution Posterior Pituitary:** 1 cc. ampuls. Preserved with 0.4 per cent phenol.

**THE UPJOHN COMPANY**

**Solution Posterior Pituitary:** 0.5 cc., 20 cc. vials and 1 cc. ampuls. Preserved with 0.4 per cent chlorobutanol.

**U. S. STANDARD PRODUCTS CO.**

**Solution Posterior Pituitary:** 0.5 cc. and 1 cc. ampuls and 10 cc. and 30 cc. vials. Preserved with 0.4 per cent chlorobutanol.

**WARREN-TEED PRODUCTS COMPANY**

**Solution Posterior Pituitary:** 10 cc. rubber capped vials. Preserved with 0.5 per cent chlorobutanol.

**THE WILSON LABORATORIES**

**Solution Posterior Pituitary:** 0.5 cc. and 1 cc. ampuls. Contains chlorobutanol, 0.5 per cent, as a preservative.

## **Placenta**

### ***Gonadotropic Substances***

Three types of biological substance which stimulate the gonads of either sex are to be distinguished. The fundamental physiological gonadotropic hormone of the normal animal body is produced by the anterior pituitary. The chemical nature of this material is unknown, and there is still debate as to whether there are one, two, or more pituitary gonadotropic hormones.

The serum of the pregnant mare contains a gonadotropic substance, which acts in a manner very similar to the preparations made from the anterior lobe. This substance is susceptible of refinement to a point where very little inert protein accompanies the active gonadotropic substance. It is probable that only one active compound is involved. An international unit of this substance has been defined by the special committee of the League of Nations, by comparison with a dry powder preparation supposed to be of stable potency. No preparation of this material is accepted by the Council.

The urine of pregnant women contains a gonadotropic substance which is distinct from that in the serum of the pregnant

mare in several respects. The latter substance does not pass out into the mare's urine in appreciable amounts, whereas the urine of pregnant women contains abundant amounts of the hormone, which is termed *chorionic gonadotropic substance*.

In rodents injection of pregnancy urine, or certain extracts thereof, induces follicular growth and corpus luteum formation. When the gonadotropic activity of pregnancy urine was first demonstrated by Zondek, it was considered that the responsible substance was secreted by the anterior pituitary. At the time, the concept was advanced that this gonadotropin consisted of two hormones—prolan A, the follicle stimulating hormone, and prolan B, the luteinizing hormone—on the basis of its effect in the rat, mouse and rabbit. Further experimentation, however, has revealed that this substance is a single entity and not composed of two factors, that it arises from the placenta rather than from the pituitary, and that it differs fundamentally from the gonadotropins of the anterior lobe. This substance is the basis of the Aschheim-Zondek test for the diagnosis of pregnancy.

A significant physiological difference between chorionic gonadotropin and preparations from the anterior pituitary is the inability of the former to stimulate to any appreciable extent the ovary of the monkey or the human being. Injection of chorionic gonadotropin into primates will not induce follicular growth or corpus luteum formation. On the contrary, reliable investigators have observed definite degenerative changes in the ovaries of women and monkeys treated with this substance. In addition, no clearcut endometrial responses have been observed in primates treated in this manner, which indicates conclusively the inability of this substance to stimulate the growth of normal ovarian structures.

The physiological action of chorionic gonadotropin is not limited to the female, but it exerts a definite effect on the male reproductive organs. It is generally agreed that this substance acts on the interstitial cells of the testes, causing them to elaborate the androgenic hormone of the testis, which in turn induces growth of the accessory sex organs. This substance is effective in male monkeys and human beings. Among the reactions induced in the monkey is the descent of the testes in the prepuberal animal. In some animals there may be some increase in the size of the seminiferous tubules, but there is little if any effect on the germinal epithelium. Spermatogenesis is, however, maintained by chorionic gonadotropin in recently hypophysectomized rats, but it is not restored after atrophy or induced in normal immature rats.

The therapeutic application of chorionic gonadotropin has covered a wide range of conditions. Many of the trials have been on an unsound or improperly conceived basis. Its use in the treatment of ovarian disturbance, for example, has no scientific rationale at the present time, although when it was first introduced for the treatment of these dysfunctions the physiological basis for therapy appeared excellent.

**CHORIONIC GONADOTROPIN.**—**Choriogonin-Lake-side.**—**Follutein-Squibb.**—**Korotrin-Winthrop-Stearns.**—The water-soluble gonadotropic substance obtained from the urine of pregnant women. It is a glycoprotein containing about 12 per cent of galactose. This preparation is standardized in international units. One international unit equals 0.1 mg. of a standardized powder (see Council Report, *J. A. M. A.* 113: 2418 [Dec. 30] 1939).

*Actions and Uses.*—Its use is recommended in the treatment of cryptorchidism where there are no anatomic lesions causing obstruction of the testicular descent. The diagnosis of an anatomic lesion can often be made in this manner where this therapy fails. Thus the surgical treatment of cryptorchidism may be instituted at an early age when it is found that hormonotherapy cannot induce descent. Injections should not be prolonged after six to eight weeks if no descent is obtained, since excessive therapy may result in undesirable responses of precocious puberty and possibly other harmful reactions.

The diagnosis of cryptorchidism should not include those cases which have been termed pseudocryptorchids, in which the testes are maintained in the inguinal canal as the result of reflex muscular spasm. It will be found that the testes return to the normal scrotal position on gentle handling and warmth.

Chorionic gonadotropin therapy in other disorders is still considered experimental because of the lack of convincing data. The treatment of hypogonadism in the adult is considered experimental at the present time. Its value in the treatment of uterine bleeding of functional nature is also as yet unproved, although numerous reports on this therapy have appeared in scientific publications. There is less enthusiasm for this therapy at the present time than there was several years ago. Considerable disagreement exists among the various investigators regarding the type of bleeding benefited by chorionic gonadotropin therapy.

*Dosage.*—The usual dose in treating cryptorchidism is from 200 to 500 international units two to three times a week. Long-continued injections may be dangerous and treatment should not be maintained after eight weeks in the absence of progressive descent. Therapy should be discontinued on the development of signs of precocious maturity.

*Preparation.*—

\* Chorionic gonadotropin is prepared from the urine of normal pregnant women by precipitating the active principle from the urine by addition of ethyl alcohol to give a concentration of more than 85 per cent alcohol, extracting the hormone from the precipitate with dilute alkaline water, and then salting out the active principle from this solution with ammonium sulfate. Further purification is made by fractionating in 50 per cent alcohol at the isoelectric point of impurities, which are removed by centrifuging. The active principle is obtained by raising the alcohol concentration to 85 per cent. The precipitate is removed by filtration and dried. The product is dissolved in water, further purified by fractional precipitation, sterilized by filtration and dried. The final material is

assayed biologically on infantile rats and compared in this procedure to the International Standard powder. The product is then diluted with sterile sucrose until its biologic activity is equal to that of the International Standard.

GEORGE A. BREON & Co., INC.

**Chorionic Gonadotropin:** 1,000 and 5,000 international units, 10 cc. vials. A powdered preparation of chorionic gonadotropin packaged in vials which, when treated with the accompanying 10 cc. of phosphate buffer solution, furnishes solutions having a potency of 100 and 500 international units per cubic centimeter, respectively.

**Chorionic Gonadotropin:** 1,000 international units and 5,000 international units, 10 cc. vials. A powdered preparation which, when diluted with the accompanying 10 cc. vial of sterile distilled water containing 0.2 per cent *meta*-cresol, provides a solution having a potency of 500 or 1,000 international units, respectively, per cc.

**Chorionic Gonadotropin:** 10,000 international units, 10 cc. vials. A powdered preparation of chorionic gonadotropin packaged in vials which, when treated with the accompanying 10 cc. ampul of phosphate buffer solution, furnishes a solution containing 10,000 international units.

COLE CHEMICAL CO.

**Chorionic Gonadotropin:** 1,000 and 5,000 international units, 10 cc. vials. Powdered preparations of chorionic gonadotropin which, when diluted with the accompanying 10 cc. vial of sterile distilled water containing 0.2 per cent *meta*-cresol, provide solutions having a potency of 100 and 500 international units per cc., respectively.

LAKESIDE LABORATORIES, INC.

**Chorionic Gonadotropin:** Bulk ampuls containing 2,000,000 and 5,000,000 international units.

Manufactured by license under U. S. patent 1,910,298.

**Choriogonin (Powder):** Bulk.

**Choriogonin:** 100 international units and 500 international units, 1.5 cc. vials. Vials containing a powdered preparation of chorionic gonadotropin with urea and sodium phosphate which when diluted with the accompanying 1.5 cc. of sterile distilled water, containing 0.5 per cent phenol, provide a solution having a potency of 66 or 330 international units per cc.

**Choriogonin:** 1,000 international units, 5,000 international units and 10,000 international units, 10 cc. vials. Vials containing a powdered preparation of chorionic gonadotropin with urea

and sodium phosphate which when diluted with the accompanying 10 cc. of sterile distilled water, containing 0.5 per cent phenol, provide a solution having a potency of 100, 1,000 or 5,000 international units per cc.

U. S. trademark 419,102.

**SHARP & DOHME, INC.**

**'Lyovac' Chorionic Gonadotropin:** 500 international units, 5 cc. A powdered preparation which, when diluted with the accompanying 5 cc. of sterile distilled water containing 0.35 per cent of phenol, provides a solution having a potency of 100 international units per cubic centimeter.

**'Lyovac' Chorionic Gonadotropin:** 1,000 international units, 10 cc. A powdered preparation which, when diluted with the accompanying 10 cc. of sterile distilled water containing 0.35 per cent of phenol, provides a solution having a potency of 100 international units per cubic centimeter.

**'Lyovac' Chorionic Gonadotropin:** 2,500 international units, 5 cc. A powdered preparation which, when diluted with the accompanying 5 cc. of sterile distilled water containing 0.35 per cent of phenol, provides a solution having a potency of 500 international units per cubic centimeter.

**E. R. SQUIBB & SONS**

**Follutein (Powder):** Bulk.

**Follutein:** 1,000 international units, 5,000 international units and 10,000 international units. Vials containing a powdered preparation of chorionic gonadotropin which, when diluted with the accompanying 10 cc. of sterile distilled water containing 0.5 per cent of phenol, provides a solution having a potency of 100, 500 and 1,000 international units per cubic centimeter respectively.

Manufacture licensed under U. S. patent 1,910,298.

**WINTHROP-STEARN, INC.**

**Korotrin:** 100 international units, 500 international units, 1,000 international units and 5,000 international units, 100 and 500 international units supplied in 2 cc. ampuls. A powdered preparation of chorionic gonadotropin admixed with sucrose which, when diluted with the accompanying 2 cc. of sterile distilled water containing 0.2 per cent of *meta*-cresol, provides a solution having a potency of 50 international units or 250 international units per cubic centimeter respectively. Marketed in boxes of 5 ampuls with 5 ampuls Korotrin diluent and in boxes of 25 ampuls without diluent. 1,000 international units supplied in 10 cc. vials: a powdered preparation of chorionic gonadotropin admixed with sucrose which, when diluted with the accompanying 10 cc. of sterile distilled water containing 0.2 per

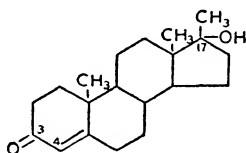
cent of *meta*-cresol, provides a solution having a potency of 100 international units per cubic centimeter. Marketed in packages containing 1 or 10 vials with 1 or 10 bottles Korotrin diluent. 5,000 international units supplied in 10 cc. vials: a powdered preparation of chorionic gonadotropin admixed with sucrose which, when diluted with suitable amounts of the accompanying 50 cc. of sterile distilled water containing 0.2 per cent *meta*-cresol, provides solutions having a potency of 100 or 500 international units per cubic centimeter. Marketed in packages containing 1 vial with 1 bottle of Korotrin diluent.

U. S. trademark 365,943.

### Testes

Testosterone, or testicular hormone, has been isolated from testicular tissue and is said to be secreted by the interstitial cells. It is responsible for the development and maintenance of the accessory male organs and characteristics. Following castration in the male, seminal vesicles, prostate and penis undergo severe atrophy. Libido is diminished and sexual activity is depressed. Injections of testosterone will restore these structures and functions to normal. They undergo regression, however, following cessation of injections. Testosterone propionate is the most effective available androgen for clinical use, the efficiency of testosterone being increased through delaying absorption from the site of injection by combination with propionic acid. Testosterone is effective by percutaneous administration. Methyl testosterone, a synthetic derivative, is much more active than testosterone when given orally. The physiological action is similar. Testosterone is not excreted in the urine, and should not be confused with the urinary androgens—androsterone and dehydroandrosterone—which have relatively little action on mammalian sexual tissue. Commercial testosterone is synthetic, and is generally marketed in the form of testosterone propionate. This substance has shown promise in the replacement therapy of eunuchoidism, but many other claims made by promoters are unwarranted or are still in the experimental stage. The beneficial effects in treating castrates or eunuchoids are present only as long as injections are continued. The cost of such treatment in the appropriate doses is often prohibitory. It has little effect in psychic impotence or as an aphrodisiac. The relief of symptoms due to prostatism has been claimed following treatment with this substance but substantial evidence in this regard is lacking. Recent reports indicate that in adequate doses this androgen is effective in treating certain ovarian dysfunctions such as menorrhagia and dysmenorrhea. Therapy in these instances is still experimental and there has been reported the induction of significant degrees of virilism in women when the amounts of androgen administered were considerable (350-400 mg. per month). Recent observations indicate that testosterone may be useful in alleviating temporarily the pain from bone metastasis of mammary carcinoma.

**METHYLTESTOSTERONE.**—U. S. P.—17-Methyltestosterone.—17-methyl- $\Delta$ -androstene-17-( $\alpha$ )-ol-3-one. The structural formula of methyltestosterone may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Methyltestosterone and Methyltestosterone Tablets.

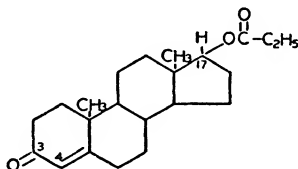
*Actions and Uses.*—Methyltestosterone may be given orally in the treatment of gonadal failure in the male. Its actions and uses are qualitatively the same as those for testosterone propionate.

*Dosage.*—The dosage and duration of methyltestosterone therapy vary considerably, depending upon the condition, its severity, previous androgenic administration and individual variation. It is usually preferable to begin therapy with a low dose, of 5 to 15 mg. daily, gradually increasing to as much as 50 mg. if higher doses appear indicated.

RARE CHEMICALS, INC.

Tablets Methyltestosterone: 10 mg. and 20 mg.

**TESTOSTERONE PROPIONATE.**—U. S. P.—The propionic acid ester of testosterone.— $\Delta$ 4-androsten-17[ $\alpha$ ]-propionate-3-one.—Testosterone propionate possesses androgenic properties. It may be prepared synthetically from cholesterol as the starting material or from testosterone isolated from bull testes. The structural formula of testosterone propionate may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Testosterone Propionate.

*Actions and Uses.*—Testosterone propionate is primarily useful to supply testicular hormone for the treatment of deficiency

or absence of this internal secretion of the male. It may therefore be of value in the treatment of prepuberal and postpuberal eunuchoidism or hypogonadism (deficiency states) and in post-castration or other cause of eunuchism. In the latter instances treatment must be regarded as replacement therapy and is of benefit only as long as it is continued.

Its use in eunuchoidism is intended to promote prepuberal development of primary and secondary sexual characteristics or to relieve postpuberal constitutional symptoms attributable to deficient secretion. It is unwise to stimulate full sexual maturity in youths who are psychologically and otherwise physically unprepared for adult life. In eunuchoidism not due to primary testicular hypoplasia, efforts to eliminate secondary etiologic factors should take precedence over the use of androgens.

Atrophy of accessory male structures that follows castration or is associated with eunuchism may also be effectively prevented or these organs restored to normal and maintained by continuous substitution therapy. However, continued administration of testosterone may induce azoospermia even though no men- tion of permanent suppression has yet appeared.

The use of testosterone in cryptorchism is subject to certain qualifications: for example, hormonal therapy cannot be effective in this condition, when there is an anatomic lesion causing obstruction of testicular descent.

*Dosage.*—Testosterone propionate is administered intramuscularly in doses ranging from 5 to 50 mg. from two to six times weekly, depending on the response obtained. To induce pubescence in eunuchoidism, 10 mg. increased as indicated to 25 mg. three times weekly, may be employed over a period of several weeks. To relieve constitutional symptoms as little as 5 mg. at similar intervals may be sufficient. Depending on the condition and the effect desired, the maintenance dose must be determined in each individual case. Priapism is indicative of excessive dosage, and its production is an indication for temporary withdrawal of the drug. There has been reported the induction of significant degrees of virilism in women when the amounts of an androgen administered were considerable (350-400 mg. per month). Testosterone propionate has a standard potency of 50 international capon units per milligram and is usually dissolved in oil for intramuscular injection.

#### RARE CHEMICALS, INC.

**Solution Testosterone Propionate in Oil:** 1 cc. ampuls of 5 mg. per cc., 10 mg. per cc and 25 mg. per cc., equivalent to 250, 500 and 1,250 international capon units per cc. respectively in sesame oil.

**Solution Testosterone Propionate in Oil with Benzyl Alcohol 3%:** 25 mg., 10 cc. vials; 50 mg., 6 cc. vials.



## Thyroid

**THYROID-U. S. P.**—"The cleaned, dried, and powdered thyroid gland previously deprived of connective tissue and fat. It is obtained from domesticated animals that are used for food by man.

"Thyroid contains not less than 0.17 per cent and not more than 0.23 per cent of iodine in thyroid combination, and must be free from iodine in inorganic or any form of combination other than that peculiar to the thyroid gland. A desiccated thyroid of a higher iodine content may be brought to this standard by admixture with a desiccated thyroid of a lower iodine content or with lactose or sodium chloride." *U. S. P.*

For description and standards see the U. S. Pharmacopeia under Thyroid and Thyroid Tablets.

*Actions and Uses.*—See under Thyroxin-U. S. P.

*Dosage.*—60 mg. daily for ten days. The dosage should be increased very gradually until improvement is as much as desired. Probably it is not wise to increase the doses at intervals of less than two weeks. The maximum daily dosage for maintenance in myxedema seldom exceeds 0.24 Gm. Administration should be discontinued if toxic symptoms appear. Thyroid usually is given in tablets. There is no evidence that coated tablets are of superior value.

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## CHAPTER XVIII

# Agents Used in Metabolic Disorders

In this chapter will be found descriptions of two groups of substances used in the treatment of metabolic disorders: (1) substances that have a special influence on metabolism, like the effect of thiouracil and derivatives on the activity of the thyroid gland; (2) substances that are administered in order that they may be themselves metabolized. The latter include dextrose, amino acids, salts of calcium, certain compounds of iodine and lipotropic agents.

Compounds of iodine for systemic use are described in the chapter on Unclassified Therapeutic Agents; those employed only as contrast media for roentgenography or other diagnostic procedures will be found in the chapter on Diagnostic Aids. Insulin and thyroid preparations, important as metabolic agents, are classified with endocrine substances in the chapter on Hormones and Synthetic Substitutes.

## PROTEIN AND AMINO ACID PREPARATIONS

Protein and amino acid preparations may be conveniently divided into two general classes: (1) mixtures of those amino acids considered essential to human nutrition that are used to combat protein deficiency imposed by severe illness or starvation; (2) individual amino acids that may be used for specific therapeutic purposes.

Preparations in the first class include (a) hydrolysates of protein or sources of protein prepared by various methods of artificial digestion designed to provide adequate amounts of the essential amino acids, and (b) mixtures of synthetic amino acids. Preparations in the second class include any of the individual amino acids that may be specifically indicated for the treatment of disease. Aminoacetic acid (glycine) formerly used in the treatment of myasthenia gravis and histidine which has been tried for the treatment of peptic ulcer are examples of this type though neither are currently recognized to be of specific value in these conditions. Neither methionine nor lysine, although promising for the treatment of liver disease, have been definitely established to be of specific therapeutic value for that condition.

While mixtures of the essential amino acids are presently recognized to exert a favorable antacid and nutritive effect in pep-

tic ulcer, their primary purpose is to supply dietary nitrogen in readily assimilated form when there is serious interference with the intake, digestion or absorption of dietary protein. There is no evidence that the addition of amino acids to foods will accomplish anything that cannot be accomplished by proper use of proteins as they occur naturally in the diet when there is no such interference.

The amino acids that are now regarded as indispensable for protein synthesis in adult man comprise those which the body is itself unable to synthesize and are generally listed as follows: phenylalanine, tryptophane, methionine, lysine, leucine, isoleucine, threonine, valine, histidine and arginine. These ten amino acids or their precursors are usually provided in mixtures intended for protein replacement in human beings but there is some doubt at present about the indispensability of histidine and arginine in adult man.

As yet there is insufficient information on which to set up exact dosage estimates for the amino acids that are prescribed to meet protein needs of the body. The daily requirements for the individual amino acids are under investigation and there are indications that these range from 0.3 to 5 Gm. each per day. Until more is known of human requirements, amino acid preparations must be given in sufficient quantities to provide every essential constituent in substantial amounts. This may be based on the commonly recommended optimum daily intake of total dietary protein: 1 Gm./Kg. of body weight, or about 70 Gm. daily for the average adult man. This figure is based on the fact that on a mixed diet the average protein intake necessary to maintain nitrogen balance has been found to be about 45 grams. There are wide variations in individual requirements and also wide variations in the biologic value of proteins from different sources, but it is estimated that the amino acid requirements will ordinarily be met on a diet containing 70 Gm. of protein.

Amino acid mixtures have appeared on the market in various forms: protein hydrolysates or hydrolytic products of good sources of protein in solution or powdered form for oral administration or intravenous injection; mixtures of amino acids in tablet form; synthetic amino acids in tablet form; synthetic amino acids combined with vitamins in tablets and elixirs; protein meals for use in tablets or food fortification. Most tablets or elixirs supply insignificant amounts for rational use in human nutrition.

Thus far, the Council considers as acceptable for nutritional purposes only those mixtures that provide adequate amounts of each of the essential amino acids. For the present, and until more evidence becomes available, the Council restricts acceptance of such amino acid mixtures for either oral or intravenous administration to hydrolysates of suitable pure proteins (such as casein) or good sources of protein (such as blood) in which more than 50 per cent of the total nitrogen present is in the form of alpha amino nitrogen. This minimum degree of hy-

hydrolysis is considered essential to justify the designation of such products as hydrolysates and to reduce the non-antigenic properties of the mixtures used for intravenous injection and those used orally for infants and children who may be allergic to protein of the diet. The Council requires that evidence of non-antigenicity for each product should be submitted. The Council has permitted the addition of carbohydrate to such hydrolysates in proportions suitable for injection. The Council has not, as yet, accepted preparations containing added vitamins or other substances considered essential for adequate nutrition pending adequate justification for such preparations.

Hydrolysates of pure proteins such as casein, lactalbumin and fibrin are properly described as "protein hydrolysates" and are defined under this general heading in the monograph below. They may be designated as "Casein (Lactalbumin, Fibrin) Hydrolysate." Hydrolysates of good sources of protein such as blood, liver and yeast are distinguished from pure protein hydrolysates and will be individually described under separate generic designations appropriate to indicate their respective derivation, e.g., Blood (Liver, Yeast) Hydrolysate. Restoration or addition of amino acids to hydrolysates should be limited to those considered "essential" for human nutrition and should be sufficient to furnish the equivalent of the biologically active form in an amount proportionate to the original source, or sufficient to meet actual requirements if the quantity needed is known. Products to which one or more amino acids have been restored or added or in which one or more of them have been at least partially removed should be designated as "Modified Casein (Liver, etc.) Hydrolysate." When carbohydrate such as dextrose has been added, the designation of such preparations should be expanded to indicate the carbohydrate component, e.g., "(Modified) Casein Hydrolysate with Dextrose ( ) per cent." When such products are supplied in the form of solution for intravenous injection, the designation should be prefixed by the word "Solution" and include the per cent of hydrolysate provided, e.g., "Solution Casein Hydrolysate 5 per cent (with Dextrose 5 per cent)." Such designations do not preclude, but should be adequately displayed with, acceptable trademark names. The Council requires that all hydrolysates be labeled with the appropriate generic designation (to include dextrose or other suitable carbohydrate when this is added), the identity of the protein or source of protein from which they are derived when this is not declared in the descriptive designation, the method of hydrolysis (acid, enzymatic or other), the nature of modification in amino acid content after hydrolysis (if any), the per cent of each amino acid or its equivalent that is present, and the percentage of alpha amino nitrogen that is represented in relation to the total nitrogen content of the mixture. Council consideration of hydrolysates for acceptance is further predicated on adequate rat growth studies to demonstrate nutritive value and in the case of intravenous products, also on adequate clinical evidence to demonstrate

freedom from antigenic, pyrogenic and toxic properties. Claims for special therapeutic purposes of hydrolysates other than for general protein deficiencies must be supported by specific scientific evidence.

Pure synthetic mixtures of amino acids for nutritional states or preparations of the individual pure amino acids used for specific therapeutic purposes will be given consideration as evidence for their usefulness is established. Preparations of intact proteins used orally as food supplements are considered to be outside the purview of the Council unless specific therapeutic value is established for such products.

**PROTEIN HYDROLYSATES—Amigen-Mead Johnson — Parnamine-Winthrop-Stearns — Protolysate-Mead Johnson.**—These are broadly defined as artificial digests of protein derived by acid, enzymatic or other hydrolysis of casein, lactalbumin, fibrin or other suitable proteins that supply the approximate nutritive equivalent of the source protein in the form of its constituent amino acids. They are required to have more than half of the total nitrogen present in the form of alpha amino nitrogen. Such preparations comprise (a) unmodified products in which there is neither partial removal nor restoration of any of the original amino acid precursors and for which the designation, "protein (or casein, etc.) hydrolysate" is restricted, and (b) modified products to which one or more amino acids have been added or one or more of them have been at least partially removed after hydrolysis and for which the designation, "modified protein (or casein, etc.) hydrolysate" is required. Other labeling requirements and the permissible modifications in amino acid composition or the addition of carbohydrate are set forth in the foregoing general statement on Proteins and Amino Acid Preparations.

*Actions and Uses.*—Parenteral preparations are useful for the maintenance of positive nitrogen balance in conditions where there is interference with ingestion, digestion or absorption of food. These conditions are most frequently encountered in severe illness and after surgical operations involving the alimentary tract. In the acute "catabolic" phase of nitrogen loss in healthy persons who become suddenly ill, it may be extraordinarily difficult to achieve nitrogen balance with the amount of hydrolysate which can be administered. The acute nitrogen loss of brief severe illness has not been shown to be pernicious, and it is debatable whether hydrolysates should be employed under these circumstances. Protein hydrolysates should not be employed as a substitute for food proteins if the latter can be adequately utilized. Intravenous injection is contraindicated in severe hepatic insufficiency and in acidosis until the latter condition is corrected. Injection may produce untoward effects such as nausea, vomiting, hyperpyrexia, vasodilatation, abdominal pain, convulsions, edema at the site of injection, phlebitis and thrombosis. Care must be exercised in looking for reactions that indicate danger. Many unfavorable reactions have been traced to inadequate care in the

cleanliness of equipment, and also to too rapid administration. Solutions that are cloudy, that contain sediment or have been opened for a previous injection should not be used. Unopened solutions should be stored in a cool place.

Claims for oral use of protein hydrolysates that are shown to be adequate nutritionally should, for the present, be limited as follows:

(1) In the diet of infants allergic to milk when the allergy cannot be met by other foods.

(2) In the treatment of peptic ulcer and in ulcerative colitis if acceptable evidence is submitted pertaining to the product concerned.

(3) Supplementing the diet in conditions in which a specially high protein intake is indicated when it is not feasible to accomplish this by use of ordinary foods.

Claims for supplementing the protein in other conditions are not permissible because there is no evidence of need for such supplementation and if it should exist it can be met by the use of ordinary foods.

*Dosage.*—See foregoing general statement on Protein and Amino Acid Preparations. Until more is known of the individual requirements for the amino acids, the dosage to be given should be designed to supply substantial amounts of all those considered essential to meet the protein needs of the body.

#### INTERCHEMICAL CORPORATION, BIOCHEMICAL DIVISION

**Elamine Lyophilized:** 60 Gm. dry protein in 850 cc. bottle. A modified casein hydrolysate prepared by acid digestion.

U. S. patent pending.

#### MEAD JOHNSON & COMPANY

**Amigen (Powder):** 454 Gm. containers.

**Solution Amigen 5% with Dextrose 5%:** Bottles of 125 cc. 500 cc. and 1,000 cc. Each 100 cc. contains 5 Gm. of Amigen and 5 Gm. of dextrose.

**Solution Amigen 10%:** 125 cc. and 500 cc. bottles. Each 100 cc. contains 10 Gm. of Amigen.

U. S. trademarks 381,523; 387,310; 422,992.

**Protolysate (Powder):** 454 Gm. containers. A casein hydrolysate prepared by digestion with fish caeca for oral administration.

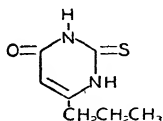
U. S. trademark applied for.

#### WINTHROP-STEARNs, INC.

**Solution Parenamine 15%:** Bottles of 100 cc. contain 15 Gm. of casein hydrolysate, consisting essentially of amino acids per 100 cc. of solution.

### Antithyroid Drugs

**PROPYLTHIOURACIL.** — 6-propyl-2-thiouracil. — The structural formula of propylthiouracil may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Propylthiouracil interferes with the formation of thyroxin by the thyroid gland. It is useful in the treatment of hyperthyroidism, thyrotoxicosis and thyroiditis. It is of no value and should not be used in other derangements of thyroid activity or in conditions not associated with hyperthyroidism.

Since propylthiouracil does not inactivate or interfere with the action of thyroxin already formed and stored in the gland, the effects of propylthiouracil medication do not appear until this store of thyroxin has been utilized. It may take several days to several weeks for the signs of decreased thyroid activity to become manifest, particularly if the patient has received previous iodine therapy.

Not all patients experience a permanent remission following propylthiouracil therapy, and the duration of treatment necessary to secure permanent relief from hyperthyroidism has not been determined. On the basis of the available information, it can be recommended only that propylthiouracil be used for pre-operative treatment or for those patients for whom operation is contraindicated. The wisdom of depending on propylthiouracil as a substitute for operative procedure can be determined only by following the results of investigations carried on for longer periods.

Propylthiouracil is capable of producing adverse reactions in some patients. The incidence and severity of these reactions are unpredictable but they occur with less frequency than following medication with the parent compound, thiouracil. The most severe complication of propylthiouracil therapy is granulocytopenia. Less severe reactions may include leukopenia, drug fever and dermatitis. The drug should be discontinued and appropriate therapy commenced immediately on the detection of signs of any of these complications.

Since the mild and the juvenile types of hyperthyroidism can frequently be controlled adequately by iodine therapy alone, propylthiouracil should not be used for these patients unless the safer form of therapy proves ineffective.

*Dosage.*—For severe cases of hyperthyroidism, initial doses of 50 mg. every eight hours appear to be effective in routine

treatment, and 50 mg. twice daily in milder cases. Iodine should be administered for two or three weeks immediately before thyroidectomy.

The effective dose of propylthiouracil should be continued until all signs and symptoms of the disease have been brought under control. Adequate maintenance dosage may best be established by determinations of the basal metabolic rate. *Patients should be instructed to cease medication and report to their physician immediately if any adverse symptoms such as sore throat, fever, coryza or malaise are experienced.*

ABBOTT LABORATORIES

**Tablets Propylthiouracil:** 25 mg. and 50 mg.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Tablets Propylthiouracil:** 50 mg.

### Calcium Compounds

Calcium compounds are used therapeutically for the purpose of overcoming calcium deficiency. The systemic action induced by calcium is dependent on the dosage and the mode of administration, which are in turn dependent upon the calcium salt that is used. Relatively insoluble salts of calcium are restricted to oral administration. Soluble salts may be given either orally or in solution by injection.

Calcium chloride is too irritating for injection other than by the intravenous route and orally produces somewhat more gastric irritation than other soluble compounds. Except that large doses may induce acidosis, it has one advantage in that in addition to supplying a relatively large amount of calcium (27 per cent), it is an acid-producing salt that by intravenous injection further favors the increase of ionized calcium in hypocalcemic tetany by reducing the pH of the blood. For the same reason other acid-producing diuretic compounds such as ammonium chloride are sometimes concomitantly administered with the use of less irritant alkaline calcium salts in the treatment of hypocalcemia.

The gluconate and levulinate salts, containing 9 and 13 per cent calcium respectively, are relatively nonirritating for subcutaneous or intramuscular injection. Muscle necrosis, however, has followed such administration in children, so that the injection of calcium compounds into the tissues should be restricted to adults.

Calcium salts are specific in the treatment of hypocalcemic tetany. Vitamin D or parathyroid hormone may also be indicated according to the etiology involved. In severe tetany, parenteral administration, preferably intravenous, is indicated to bring symptoms under rapid control. Latent tetany or mild symptoms may be controlled by oral medication. Hydrochloric acid may increase the absorption of calcium when this is deficient.

The chloride, lactate or carbonate salts of calcium are all suitable for oral administration in doses corresponding to their



percentage of calcium content. Chemical compounds represented by such salts as the citrate, oxylate or phosphate, that are capable of precipitating or combining with ionized calcium of the blood when taken in large amounts, should probably be avoided in the presence of hypocalcemia since they may convert a latent tetany into active convulsions. The administration of large amounts of bicarbonate or persistent vomiting would have the same effect by increasing the  $pH$  of the blood. Tribasic calcium phosphate has been administered orally when phosphorus as well as calcium is deficient, but its use should probably be restricted to less severe forms of calcium deficiency.

Calcium has been used to shorten the coagulation time of the blood, for the treatment of certain types of edema and ascites, as a cardiac stimulant, to relieve the pain of intestinal, biliary and renal colic, and in the treatment of various dermatoses, allergic conditions and tuberculosis. Calcium salts have also been reported to be effective in the prevention of arsphenamine reactions and to diminish the toxicity of carbon tetrachloride. It has been reported that a relative deficiency of calcium is associated with insensitivity of the uterus to oxytocics and that calcium potentiates the action of the latter agents. In none of the foregoing conditions, however, is there sufficient clinical evidence for the therapeutic use of calcium and none is ordinarily associated with a demonstrable deficiency. Such uses are mostly empirical and have not been substantially supported by experimental evidence.

Calcium deficiency is not a factor in clinical alterations of the bleeding or clotting time of blood, and an excess has been shown experimentally to prolong rather than shorten the coagulation time. The supposed antiedemic effect of calcium by decrease of cellular membrane permeability has not been demonstrated in the tissues, and the presumed antispasmodic effect on smooth muscle has not been confirmed by experimental observations. The cardiac and uterine effects of calcium are dependent on optimum concentrations, so that the role of calcium in regulating the muscular functions of these structures has little or no clinical application. Hypercalcemia has been reported to increase the toxicity of digitalis, but this is largely theoretical. Intravenously, overdoses may fatally paralyze the heart and the central nervous system; intravenous injection should be made very slowly.

The therapeutic use of calcium in the absence of demonstrable deficiency of that cation in the blood or extracellular fluids is considered irrational. In ordinary dietary deficiency the administration of calcium compounds should not take precedence over a remedial diet well balanced in the choice of foods rich in calcium.

**AFENIL-Bilhuber-Knoll.**— $\text{CaCl}_2 \cdot 4(\text{NH}_2)_2\text{CO}$ .—Afenil is a molecular compound of calcium chloride and urea.

For tests and standards, see Section B.

**Actions and Uses.**—Afenil has the actions of calcium chloride. It is claimed that afenil solutions, when administered intravenously, are better tolerated and less irritating than solutions of calcium chloride.

**Dosage.**—Afenil is marketed in ampuls containing 10 cc. of a 10 per cent solution of Afenil. Each injection consists of the entire contents of one ampul.

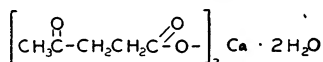
BILHUBER-KNOLL CORP.

**Solution Afenil 10%:** 10 cc. ampuls containing a solution equivalent to 0.11 Gm. Ca.

U. S. trademark 170,032. German patent 306,804.

**CALCIUM LEVULINATE-N.F.**—"A hydrated calcium salt of levulinic acid and contains not less than 97.5 per cent and not more than 100.5 per cent of  $(\text{CH}_3\text{CO}(\text{CH}_2)_2\text{COO})_2\text{Ca}$  calculated on a dry basis, the loss on drying being determined on a separate portion by drying at 105 C. for 24 hours."—N. F.

The structural formula may be represented as follows:



For description and standards see The National Formulary under Calcium Levulinate and Calcium Levulinate Ampuls.

**Actions and Uses.**—Calcium levulinate is used to obtain the therapeutic effects of calcium. It may be administered orally or intravenously and is virtually nonirritant for subcutaneous or intramuscular injection.

**Dosage.**—By injection, for adults, 1 Gm. daily or on alternate days; for children, 0.2 to 0.5 Gm. Orally, for adults, 4 to 5 Gm. three times a day; for children, 1 to 2 Gm. three times a day.

CHEMO PURO MANUFACTURING CORP.

**Calcium Levulinate (Powder):** 30 Gm. and 480 Gm. bottles.

THE J. F. HARTZ COMPANY

**Solution Calcium Levulinate 10%:** 1 Gm. in 10 cc. ampuls.

PAUL LEWIS LABORATORIES, INC.

**Calcium Levulinate (Powder):** Bulk. Packaged in units of 500 Gm. and multiples thereof.

CARROLL DUNHAM SMITH PHARMACAL CO.

**Solution Calcium Levulinate 10%:** 1 Gm. in 10 cc. ampuls.

## Iodine Compounds for Systemic Use

These are typified by sodium iodide and potassium iodide. The mechanism of their action is not clearly understood. The most definite results are seen in the rapid absorption of certain inflammatory exudates and especially of the gummatous lesions

of tertiary syphilis. Lesions of this type in bone, skin, brain, or other organs diminish or disappear under adequate doses of the drug. In actinomycosis and sporotrichosis the action of iodide formerly was regarded as almost specific, but has little curative value and has been superseded by more promising agents. The iodide ion is not germicidal.

The beneficial effect of iodides in aneurysm is probably limited to the absorption of syphilitic deposits in the vessel wall. The iodides do not directly lower blood pressure. They may tend to affect the production of thyroxin and may thus exert an indirect effect on metabolism. Iodides in very small amounts are effective in the prophylaxis of simple endemic goiter, and in controlling the symptom of hyperthyroidism in preparation for operation.

Iodine compounds with proteins and fats have been introduced with claims that they are less irritating to the digestive tract and that they are less inclined to set up the disagreeable symptoms of iodism, such as coryza and skin eruptions. Experience confirms, in a measure, the former claim, but the latter is misleading. Iodism is probably a necessary manifestation of the full physiological activity of the drug. If, therefore, a preparation consistently fails to elicit these characteristic symptoms, it may be presumed that the amount of the drug absorbed is insufficient to produce the full effects, such as are required in the treatment of syphilis. It may suffice, however, in conditions for which a milder action is desired. Clinical observations establish the fact that the organic iodides, in the dosage ordinarily employed, are weaker than full doses of the inorganic forms.

*Warning:* The use of iodides should be restricted to oral administration. The dangers attending intravenous injection of sodium iodide, i.e., acute and violent iodism, colloidoclastic shock and pulmonary edema, outweigh the doubtful advantages to be gained by this route of administration.

**METHENAMINE TETRAIODINE.**—**Siomine-Pitman-Moore:**—Hexamethylenetetramine tetraiodide.—Methenamine tetraiodide.—Siomine contains 78.5 per cent of iodine.

For tests and standards, see Section B.

*Actions and Uses.*—Methenamine tetraiodine is decomposed in the intestine with formation of hexamethylenetetramine and iodide, the rate of absorption and excretion being essentially the same as that of inorganic iodides. It, therefore, produces the effects of ordinary iodides, from which it differs only in that it can be administered in solid form.

No therapeutic claims are made for the hexamethylenetetramine component of methenamine tetraiodine, which serves only to render the substance insoluble. While ordinarily the hexamethylenetetramine content of methenamine tetraiodine may be ignored, the drug should be discontinued if any signs of hexa-

methylenetetramine intolerance arise, such as vesical irritation or hematuria.

*Dosage.*—Orally, 0.3 Gm. methenamine tetraiodine is best administered in capsule form during or immediately following meals.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Capsules Siomine:** 60 mg., 0.13 Gm. and 0.3 Gm.

U. S. patent 1,226,394 (May 15, 1917; expired). U. S. trademark 107,998.

### *Iodized Fats and Fatty Acids*

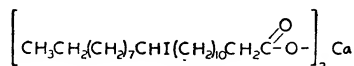
Iodized fats and iodized fatty acids produce, in general, the same systemic effects as ordinary (inorganic) iodides; their iodine, however, is more slowly absorbed and excreted, and therefore more persistently retained, especially in tissues rich in lipoids, such as the nervous structures.

Iodized fats and iodized fatty acids produce in general the same systemic effects as ordinary (inorganic) iodides; but their iodine is more slowly absorbed and excreted, and therefore more persistently retained; especially in tissues rich in lipoids, such as the nervous structures.

The iodized fats and fatty acids generally pass the stomach unchanged, and are saponified and absorbed in the small intestine, like ordinary fats. They are then deposited for the most part in lipid tissues, where they are gradually oxidized, yielding inorganic iodide which is given off to the blood and excreted. The iodine content of the blood is thus maintained more uniform than when inorganic iodides are administered.

It is conceivable that iodized fats and fatty acids have therapeutic advantages over ordinary iodides when a gradual, long-sustained iodide action is desired, but the clinical evidence is not decisive. The doses used in these conditions, as a rule, are not irritating to the stomach and are not likely to produce iodism. Hypodermic injections remain unabsorbed for long periods and do not produce systemic actions, except in very hypersensitive individuals, for instance in tuberculosis.

**CALCIUM IODOBEHENATE-U. S. P.**—Sajodin-Winthrop-Stearns.—Calcium Monoiodobehenate.—“Consists principally of calcium monoiodobehenate  $[(C_{21}H_{42}IOO)_2Ca]$  and contains, when dried at 100 C. for two hours, not less than 23.5 per cent of I [iodine].”—U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Calcium Iodobehenate.

*Actions and Uses.*—Calcium iodobehenate is used as a substitute for the inorganic iodides. See general article, Iodized Fats and Fatty Acids.

*Dosage.*—0.5 Gm.

WINTHROP-STEARNs, INC.

**Sajodin (Powder):** Bulk.

**Tablets Sajodin:** 65 mg. and 0.52 Gm.

U. S. patent 839,509 (Dec. 25, 1906; expired). U. S. trademark 61,730.

**IODINATED CASTOR OIL.**—**Riodine (Astier)-Gallia Labs.**—A 66 per cent solution in oil of an iodine addition product of castor oil prepared by treating castor oil with hydrogen iodide. Iodinated castor oil contains about 17 per cent of iodine.

For tests and standards, see Section B.

*Actions and Uses.*—Iodinated castor oil is used as a substitute for the inorganic iodides. See general article, Iodized Fats and Fatty Acids.

*Dosage.*—From 0.4 to 1.2 Gm. per day, in pearls, taken after meals. Supplied only in the form of pearls.

GALLIA LABORATORIES, INC.

**Pearls Riodine:** 0.2 Gm.

U. S. trademark 86,974.

**IODOBRESSID.**—**Lipodine-Ciba.**—See Iodobrassid under Iodized Oils in the chapter on Diagnostic Aids.

*Dosage.*—From 0.3 to 0.6 Gm., daily or in acute cases from 1.2 to 1.8 Gm. daily. Lipiodine tablets should be masticated before swallowing.

CIBA PHARMACEUTICAL PRODUCTS, INC.

**Tablets Lipiodine:** 0.3 Gm. (uncoated).

U. S. patent 1,024,171 (April 23, 1912; expired). U. S. trademark 81,554.

**IODIZED OIL-U. S. P.**—**Lipiodol, 40% Iodine-Fougera.**—See Iodized Oils in the chapter on Diagnostic Aids.

*Dosage.*—Two to five capsules daily after meals.

E. FOUGERA AND COMPANY, INC.

**Capsules Lipiodol (40% Iodine):** 0.5 Gm. Each gelatin capsule contains iodized oil, equivalent to 0.2 Gm. of iodine.

U. S. trademark 196,499.

**ORIDINE-Lilly.**—The calcium salt of the iodized fatty acids of cottonseed oil. It contains from 23 to 25 per cent of iodine in organic combination.

For tests and standards, see Section B.

**Actions and Uses.**—Oridine is used as a substitute for the inorganic iodides. See general article, Iodized Fats and Fatty Acids.

**Dosage.**—The iodine content of Oridine 1 Gm. is approximately equivalent to sodium iodide 0.28 Gm. and to potassium iodide 0.31 Gm. When used for the prophylaxis of goiter, 10 mg. to 30 mg. per day is given until 40 doses have been taken.

ELI LILLY AND COMPANY

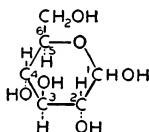
**Oridine (Powder):** Bulk.

**Tablets Oridine:** Equivalent to 10 mg. iodine. This dosage form is used only for prophylaxis against goiter and for the treatment of simple goiter.

U. S. trademark 185,838.

## Dextrose

**DEXTROSE-U. S. P.**—*d-Glucose*.—"A sugar usually obtained by the hydrolysis of starch." U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Dextrose, Dextrose Injection and Dextrose and Sodium Chloride Injection.

**Actions and Uses.**—Dextrose is a readily absorbable food. Its solution, which are being extensively used in modern therapy, may be administered for parenteral alimentation by hypodermic or intravenous injection. Alone or in combination with various salt solutions, they are used to supply fluid, to sustain the blood volume temporarily, or to produce diuresis. Primarily they are intended to supply dextrose to the patient without disturbing the gastro-intestinal tract. The strength of the solution, the medium (distilled water, isotonic solution of sodium chloride, or Ringer's solution), as well as the total quantity and route of administration must be varied to meet the indications of the individual case.

Subcutaneous injections are necessarily low in dextrose content (2.5 per cent in isotonic solution of sodium chloride); intravenous solutions may vary in strength from 5 to 50 per cent of dextrose. Slow rate of flow is essential to the proper administration of these solutions and is especially important in cases of hemorrhage which are not entirely controlled. If it is necessary to supply very large amounts of dextrose to the individual in a relatively short time, small amounts of high

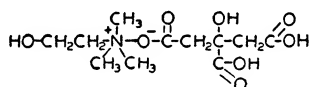
concentration are generally preferable to greater amounts of lower concentration.

Since U. S. P. dextrose contains one molecule of water of crystallization, physicians should bear in mind that a solution labeled in terms of dextrose-U. S. P. will actually contain a smaller amount of anhydrous dextrose. However, in prescribing there should be reference to hydrous dextrose in conformity with U. S. P. practice. The physician should bear in mind that in more concentrated solutions of dextrose there is considerable variation in content when comparing dextrose percentage calculated on the basis of content of the hydrous and anhydrous forms. This amounts to approximately 5 Gm. in 100 cc. in case of a 50 per cent solution. Manufacturers are encouraged to label their products in terms of per cent (W/V) of dextrose-U. S. P.

*Dosage.*—The dosage of dextrose in a single injection varies with the strength of the solution and may range between 5 and 250 Gm. with the different purposes for which the solutions are used.

### Lipotropic Agents

**CHOLINE DIHYDROGEN CITRATE.**—Trimethyl hydroxyethyl ammonium citrate.—The dihydrogen citrate of trimethyl ethanolammonium hydroxide.—The structural formula of choline dihydrogen citrate may be represented as follows:



For tests and standards see Section B.

*Actions and Uses.*—Choline dihydrogen citrate has been used in the treatment of hepatic diseases associated with decided fatty infiltration. In the experimental animal it has been demonstrated that a fatty liver can be produced by a diet free of choline and that the fatty degeneration thus produced can be cured by the administration of choline. Clinical observations in human beings suffering from a variety of diseases of the liver have not been conclusive, but the results have been sufficiently promising to warrant trial of the agent in fatty degeneration and cirrhosis of the liver in conjunction with other recognized forms of therapy. However, the results of choline therapy in advanced fibrotic cirrhosis of the liver have been disappointing.

The normal diet contains large amounts of choline, and there is no valid evidence that a pathologic state due to choline deficiency exists in man. The possibility of such a deficiency seems unlikely because of the amount of choline present in most food stuffs. In addition, it has yet to be conclusively demonstrated that choline therapy is superior to an adequate diet in the treatment of liver disease.

*Dosage.*—Two to 3 Gm. of choline dihydrogen citrate (8 cc. to 12 cc. of the 25 per cent syrup) in divided doses. Choline is always administered orally.

FLINT, EATON & Co.

**Syrup Choline Dihydrogen Citrate:** 475 cc. bottles. A flavored syrup containing 25 per cent of choline dihydrogen citrate. Each 4 cc. contains 1 Gm. of choline dihydrogen citrate.



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## CHAPTER XIX

# Parenteral Solutions

This chapter includes preparations for injection that are used to supply water, salts or ions to replace lost body fluid, combat dehydration, restore electrolyte balance, and replenish the buffer system of the blood.

Solutions of dextrose, sometimes used to combat water loss or to encourage output of fluid, and solutions of calcium salts used for hypocalcemic tetany, are described in the chapter on Agents Used in Metabolic Disorders. Preparations of plasma for intravenous injection to restore blood volume are to be found in the chapter on Serums and Vaccines.

Parenteral solutions are often warmed so that they may enter the vein at body temperature. The entire apparatus (bottle or flask, rubber tubing, connections, and needle) must be sterile and the entire line of rubber tubing, as well as the needle, must be freed of air bubbles before the needle is inserted. The area in which the needle is injected must also be adequately prepared. The intake air should be filtered by a cotton pledget or other adequate device.

The administration of these solutions should be instituted by a physician and continued under his supervision (especially intravenous injection), and must be discontinued before the container is empty. Intraperitoneal injections are not recommended because they cause distention which may be prolonged and may induce a sterile peritonitis with polymorphonuclear exudation.

Frequently apparatus used for the administration of intravenous solutions is used repeatedly. Before the apparatus is again used it must be sterilized, this sterilization process to be preceded by rinsing several times in distilled water. This should eliminate any untoward reactions which may be due to the lack of such thorough cleansing.

Many parenteral solutions are offered in special containers bearing special trademark designations. Most of these have been examined by the A. M. A. Chemical Laboratory and many formerly were described in New and Nonofficial Remedies. Included are containers bearing such names as "Vacoliter" (Baxter Laboratories, Inc., and Don Baxter, Inc.), "Saftiflask" (Cutter Laboratories), "Filtrair" (Hospital Liquids, Inc.).

### Sodium Lactate

**SODIUM LACTATE INJECTION-U. S. P.**—"A sterile solution of sodium lactate ( $\text{NaC}_3\text{H}_5\text{O}_3$ ) in water for injection.

It contains not less than 95 per cent and not more than 110 per cent of the labeled amount of  $\text{NaC}_3\text{H}_5\text{O}_3$ ."—U. S. P.

For tests and standards see the U. S. Pharmacopeia under Sodium Lactate Injection.

*Actions and Uses.*—Sodium lactate injection is approximately isotonic with the blood and is used in the treatment of acidosis (as such or combined with Ringer's solution) and for the purpose of alkalizing the urine (for instance, in the treatment of acute urinary tract infections with sulfanilamide, in the treatment of transfusion reactions with hemoglobinuria). This solution is not indicated in the acidosis associated with congenital heart disease with persistent cyanosis.

*Dosage.*—Administered subcutaneously or intravenously. Intravenous solutions should not be administered at a rate greater than 300 cc. per hour (approximately 60 drops per minute) except on specific order of the physician. It can be calculated that each 60 cc. of sodium lactate injection per kilogram of body weight may increase the sodium ion concentration of the blood plasma about 14 millimols (mM) per liter. This corresponds to a rise in bicarbonate concentration sufficient to yield an additional 33 volumes of carbon dioxide per hundred cubic centimeters of blood plasma.

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## CHAPTER XX

# Pharmaceutic and Therapeutic Aids

This chapter includes the description of substances which, though in themselves therapeutically inactive, are useful medicinally in compounding preparations containing active agents. It, therefore, includes such articles as solvents, antioxidants, emulsifying agents, water-soluble bases, or other materials that may serve as special vehicles useful in the application of therapeutic agents.

**ABSORBABLE GELATIN SPONGE.** — **Gelfoam-Upjohn.**—A sterile absorbable water-insoluble gelatin base sponge.

For tests and standards, see Section B.

*Actions and Uses.*—Absorbable gelatin sponge material, although insoluble in aqueous mediums, is absorbable and as such may be used as a surgical sponge, which may be left in place following closure of an operative wound. It is claimed that such material will be completely absorbed without inducing excessive formation of scar tissue or excessive cellular reaction in from four to six weeks. It is indicated in the control of capillary bleeding, particularly when moistened with thrombin solution.

*Dosage.*—Absorbable gelatin sponge may be applied to the bleeding surfaces in amounts sufficient to cover the area. For such purposes it should first be moistened thoroughly with sterile isotonic sodium chloride solution or thrombin solution.

### THE UPJOHN COMPANY

**Gelfoam:** Jars containing four sterile sections, 20 by 60 mm. and sterile envelopes containing a single section 80 by 125 mm.

**CARBOWAX 1500-Carbide & Carbon.**—White grade.—A mixture of polyethylene glycols, having an average molecular weight of about 550, suitable for the compounding of water-soluble ointment bases. It is a bland, water-soluble, non-volatile, odorless solid, having the consistency of a low-melting petrolatum. It is insoluble in petroleum ether but completely soluble in water at 50 C. It melts from 30-42 C., and the  $pH$  of a 5 per cent aqueous solution is about 4.6.

Trademark of Carbide and Carbon Chemicals Corporation (U. S. trademark 380,450).

**CARBOWAX 4000-Carbide & Carbon.**—A polyethylene glycol, having an average molecular weight of 3350. It is a bland, hard, white, waxy solid, which melts from 54-57 C. It is soluble to form about 60 per cent solutions in water but is insoluble in petroleum ether. The  $pH$  of a 5 per cent solution is about 6.35. It is used in compounding water-soluble ointment vehicles.

Trademark of Carbide and Carbon Chemicals Corporation (U. S. trademark 380,450).

**CARBOWAX 1540-Carbide & Carbon.**—A polyethylene glycol having an average molecular weight of about 1450. It is a bland, white waxy solid which melts from 40 to 45 C. It is soluble to form about 70 per cent solutions in water but is insoluble in petroleum ether. The  $pH$  of a 5 per cent solution is about 6.5. It is used in compounding water-soluble ointment vehicles.

Trademark of Carbide and Carbon Chemicals Corporation (U. S. trademark 380,450).

**FIBRIN FOAM.**—A sterile, dry preparation of fibrin prepared from Fraction I of citrated normal human plasma as fractionated by the method of Cohn (*J. Am. Chem. Soc.* 68:459, 1946). It complies with the requirements of the National Institute of Health of the United States Public Health Service.

For tests and standards see Section B.

**Actions and Uses.**—Fibrin foam (human) acts as a mechanical coagulant, and in combination with thrombin gives a chemical, as well as a mechanical, matrix for coagulation. It has been used in surgery of the brain, liver, kidneys, and other organs where ordinary methods of hemostasis are ineffective or inadvisable.

**Dosage.**—Apply directly to oozing surface.

#### CUTTER LABORATORIES

**Fibrin Foam and Thrombin (Human):** Packages containing a 250 mg. (6.25 to 12.55 cc.) jar of fibrin foam, a vial of thrombin (human) containing not less than 200 units, and a 20 cc. vial of isotonic sodium chloride solution.

The thrombin supplied meets the requirements of the National Institute of Health of the United States Public Health Service and is derived from human plasma.

Licensed by Research Corporation under U. S. patent 2,389,074.

**GELATIN COMPOUND PHENOLIZED.**—A mixture composed of gelatin 14 per cent, carbolic acid (phenol) 1.5 per cent, zinc oxide 5.5 per cent and glycerin 39 per cent.

**Actions and Uses.**—Gelatin compound phenolized is used in the preparation of bandages to cover chronic ulcers and unhealed secondary burns and in the preparation of pressure bandages for varicose veins when surgical treatment is not necessary.

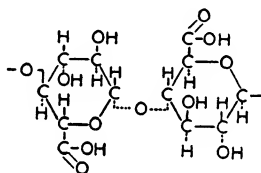
**Dosage.**—For use, the preparation is heated until it becomes liquid and is applied with a brush; over this a spiral bandage is applied and another layer of the preparation brushed on;

this is repeated until a total thickness of three layers of the bandage and four of the preparation has been applied.

SHARP & DOHME, INC.

Gelatin Compound Phenolized: Bulk.

**OXIDIZED CELLULOSE.**—Hemopak-Johnson & Johnson.—Absorbable cotton or gauze.—Cellulosic acid.—Oxidized cellulose is prepared by the nitrogen dioxide oxidation of surgical gauze or cotton. Cellulosic acid is a polyanhydroglucuronic acid having a minimal carboxyl content of 16 per cent, a nitrogen content not in excess of 0.5 per cent derived from the nitrogen dioxide used in its preparation, and a formaldehyde content not in excess of 0.5 per cent derived from the formaldehyde used in its sterilization. The generally accepted structural formula for cellulosic acid may be represented as follows:



For tests and standards see Section B.

**Actions and Uses.**—Oxidized cellulose, a specially treated form of surgical gauze or cotton, exerts an unusual hemostatic effect and possesses the property of absorbability when buried in the tissues. Its hemostatic action is dependent upon the formation of an artificial clot by cellulosic acid which has a marked affinity for hemoglobin, but does not enter per se into the physiologic mechanism of clotting. Absorbability depends on the size of the implant used, the adequacy of the blood supply to the area and the degree of chemical degradation of the material. Absorption of oxidized cellulose ordinarily occurs between the second and seventh day following implantation of the dry material, but complete absorption of large amounts of blood-soaked material may take six weeks or longer.

Oxidized cellulose is of value as an aid in surgery for the control of moderate bleeding under conditions where suturing or ligation is technically impractical or ineffective. Such situations include the control of capillary, venous or small arterial hemorrhage encountered in operations upon the biliary tract, partial hepatectomy, resections or injuries of the pancreas, spleen or kidneys, bowel resections, amputations, resections of the breast, thyroid and prostate and in certain aspects of neurologic and otolaryngologic surgery. Oxidized gauze is employed as a sutured implant or temporary packing depending on the anatomic site or structures involved. Oxidized cotton is used primarily for

neurologic surgery as unsutured packing, small portions of which may be left unremoved to control small areas of oozing from the dura or brain tissue. This material is likewise useful as temporary packing for control of secondary hemorrhage following adenoidectomy, tonsillectomy and other oral procedures and for control of alveolar bleeding following tooth extraction. Neither oxidized gauze nor cotton should be used for permanent packing or implantation in fractures because it interferes with bony regeneration and may result in cyst formation.

The hemostatic action of oxidized cellulose is not enhanced by the addition of other hemostatic agents such as thrombin which would be destroyed by the low pH of the material and it has been shown that the hemostatic action of either alone is greater than the combination. The hemostatic effect is greater when the dry material is applied, so that moistening with water or saline is not recommended. When properly used, oxidized cellulose may be closed in a clean wound without drainage, but this is hazardous whenever gross contamination is suspected or frank infection is present.

*Neither oxidized gauze or cotton should be used as a surface dressing except for the immediate control of hemorrhage, as cellulosic acid inhibits epithelialization.*

**Dosage.**—The amount of oxidized gauze or cotton used varies with the circumstances of the individual case. As a general rule, only the minimal amount required to control hemorrhage should be used. For the control of hemorrhage from the prostatic bed, this may vary from one to four 2" x 14" gauze packing strips, depending upon the extent and vascularity of the area to be packed and the technic employed. This size of oxidized gauze is particularly designed for implantation by means of mattress sutures. Gauze packing strips ½" x 2½ yds. are adapted for otolaryngologic or dental procedures; cotton pads, 2" x 6" are designed for neurologic, oral and/or dental surgical procedures.

In the event that it is desired to remove gauze or cotton from a hollow viscus or drainage site before dissolution is complete, removal can be facilitated by irrigation.

JOHNSON & JOHNSON

**Hemo-Pak Absorbable Gauze Packing Strip (4 ply):** 2" x 14" (5.08 by 35.56 cm.) and ½" x 2½ yds. (1.27 by 228.6 cm.) in sealed tubes.

**Hemo-Pak Absorbable Cotton Pad:** 2" x 6" (5.08 by 15.24 cm.) in sealed tubes.

U. S. trademark registration pending.

**PLIABLE PARAFFIN.**—Parresine-Abbott.—A mixture composed of paraffin (melting point 48 to 49 C.), from 94 to 96 per cent; gum elemi, from 0.20 to 0.25 per cent; Japan wax, from 0.40 to 0.50 per cent; asphalt, from 0.20 to 0.25 per cent, and eucalyptol, 2 per cent. To this mixture is added from 0.5 to 1.0

per cent solution of alkannin in eucalyptol and a minute quantity of gentian violet, these being employed to bring the product to a standard color. Marketed only in the form of Parresined Lace Mesh Surgical Dressing.

*Actions, Uses and Dosage.*—Nonabsorbent protective, used for the preparation of Parresined Lace Mesh Surgical Dressing.

**ABBOTT LABORATORIES**

**Parresined Lace-Mesh Surgical Dressing:** Net mesh gauze impregnated with, and containing, from 45 to 50 per cent of Parresine.

U. S. trademark 117,626.

**POLYETHYLENE GLYCOL 300-Carbide & Carbon.**—White grade.—A polymer having the general formula  $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_x\text{CH}_2\text{OH}$ , with an average molecular weight of 300. It is a white, viscous liquid, which freezes between  $-15$  and  $8^\circ\text{C}$ . It is completely miscible with water in all proportions and is useful in the compounding of water soluble ointment bases and pharmaceuticals for topical applications.

**PROPYLENE GLYCOL-N. F.**—Racemic 1,2-dihydroxypropane.— $\text{CH}_3\text{CHOH.CH}_2\text{OH}$ . "Contains not less than 97.5 per cent by weight of  $\text{C}_3\text{H}_8\text{O}_2$  [propylene glycol]."—*N. F.*

For description and standards see The National Formulary under Propylene Glycol.

*Actions and Uses.*—Propylene glycol is used for pharmaceutical purposes as a diluent. Its toxicity is similar to that of glycerin. As ordinarily employed, it may be called practically nontoxic.

**THIOUREA.**— $\text{S}:\text{C}(\text{NH}_2)_2$ .

For tests and standards, see Section B.

*Uses.*—Thiourea may be added to solutions of certain substances, e.g., Metycaine with epinephrine, in order to prevent oxidation.

**TRIETHANOLAMINE-U. S. P.**—"A mixture of alkanolamines consisting largely of triethanolamine  $\text{N}(\text{C}_2\text{H}_4\text{OH})_3$ , admixed with various amounts of diethanolamine  $\text{NH}(\text{C}_2\text{H}_4\text{OH})_2$  and monoethanolamine  $\text{NH}_2(\text{C}_2\text{H}_4\text{OH})$ . It has an alkalinity equivalent to not less than 6.7 cc. and not more than 7.2 cc. of normal acid for each 1 Gm. of Triethanolamine."—*U. S. P.*

For description and standards see the U. S. Pharmacopeia under Triethanolamine.

*Actions and Uses.*—Triethanolamine-technical is an excellent emulsifying agent for use in the preparation of ointments and other dermatologic medicaments. When added to certain preparations used on the scalp, for example, oil of cade, it facilitates their subsequent removal. Triethanolamine-technical combines

with fatty acids to form soaps with good detergent properties, which are soluble not only in water but also in gasoline, kerosene, and oils. It is claimed to have the power of increasing the penetration of oily substances and to possess a certain amount of bacteriostatic action. Rarely an individual will be encountered who is sensitive to this compound.

*Dosage.*—In the preparation of stable emulsions of fatty or vegetable oils, triethanolamine and oleic acid are first added to about one-third of the oil. Using mechanical agitation, about one-third of the water is added and stirred until a thick smooth emulsion is formed. Then with continued mechanical agitation, alternate thirds of oil and water are slowly stirred in. Emulsions may be made containing from 20-40 per cent of oil, which may be diluted with as much as five times the volume of water. For emulsions containing olive oil, the proportions based on the weight of the oil are 2.4 per cent by weight triethanolamine and 11.5 per cent oleic acid. Substantially the same proportions are used for the majority of vegetable oil emulsions, while for paraffin oil emulsions, the amount of triethanolamine should be increased to 5 per cent by weight.



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## CHAPTER XXI

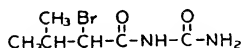
# Sedatives and Hypnotics

This chapter includes agents that act principally as depressants of the central nervous system and that may be used to induce sleep if pain is absent or to control convulsions. This group is to be distinguished on the one hand from the analgesics which are used to relieve pain, and on the other hand from the antispasmodics which act primarily to depress muscular activity. Their distinction from anesthetics is less sharp since some sedative compounds, notably the barbiturates, may be administered in doses sufficient to produce general anesthesia. Morphine and its derivatives, used mainly as analgesics, are included along with opium principles in the chapter on Analgesics.

### Compounds Containing Bromine

Synthetic compounds containing bromine have been produced with the purpose of securing the sedative action of bromide ion without the objectionable effects of the alkali bromides. These compounds split off bromide ions in the system, the decomposition being due to the oxidation of the organic substance with which it is combined; but bromine which is too firmly bound may fail to exert its typical effects. As the usual indications for bromide action in the organism require a prompt and powerful action on the cells to produce sleep, to abolish reflexes or to arrest an epileptic paroxysm, the synthetic compounds are likely to fail as substitutes for the alkali bromides because their bromide ion is liberated too slowly. The introduction of bromine into compounds already possessing hypnotic or sedative powers may result in increasing the efficiency of these compounds.

**BROMISOVALUM** — Bromural-Bilhuber-Knoll. — 2-Monobromisovalerylurea, obtained by the interaction of urea with bromisovaleryl bromide. The formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—Bromisovalum is a sedative which produces sleep in mild cases of insomnia without markedly affecting the circulation or respiration. All action by bromisovalum

is said to cease after from three to five hours. In many cases, however, the sleep caused by the preparation continues beyond the limits of its action. It is useful as a sedative and for the purpose of inducing sleep in functional nervous disease. Bromisovalum is not effective in cases of insomnia associated with pain, cough, angina pectoris or delirium.

*Dosage.*—As a sedative, 0.3 Gm., three times daily; as a hypnotic at bedtime, 0.6 Gm., which dose may be repeated if advisable during the night after three to four hours.

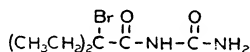
BILHUBER-KNOLL CORP.

**Tablets Bromural:** 0.3 Gm.

**Bromural (Powder):** 30 Gm. bottles.

U. S. patent 914,518 (March 9, 1909; expired). U. S. trademark 61,165.

**CARBROMAL-N. F.**—Bromodiethylacetylurea. The formula may be represented as follows:



For description and standards see The National Formulary under Carbromal.

*Actions and Uses.*—Carbromal is said to be an efficient and prompt sedative, reducing excitement and promoting sleep in conditions in which a powerful hypnotic is not required. In therapeutic doses it is said not to exert any unfavorable influence on the respiration or heart action. The sleep produced is said to be restful, dreamless and exceptionally free from unpleasant by-effects and sequelae.

Carbromal is stated to be useful as a sedative and mild hypnotic in neurasthenia, cardiac neuroses with tachycardia, chorea, mental disorders with moderate excitement, insomnia due to various internal diseases.

*Dosage.*—As a sedative from 0.3 to 0.6 Gm., given in cold water, repeated three or four times daily if necessary; as a hypnotic from 0.6 to 1.3 Gm., followed by a drink of hot, sweetened water or weak tea.

MERCK & Co., INC.

**Carbromal (Powder):**

THE UPJOHN COMPANY

**Tablets Carbromal:** 0.3 Gm.

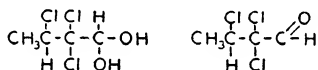
WYETH, INCORPORATED

**Tablets Carbromal:** 0.3 Gm.

### Chloral Derivatives

Chloral hydrate is still the standard hypnotic of its class; but it has the disadvantages of causing cardiac and respiratory depression in overdosage and of irritating the stomach unless diluted suitably; furthermore, it cannot be used hypodermically. Attempts to modify the drug so as to make it safer have at the same time resulted in weakening its hypnotic action. Attempts to remove its irritant action have been more successful. The chloral derivatives described below are less irritating to the stomach. Chlorobutanol can be given by hypodermic injection.

**BUTYLCHLORAL HYDRATE.**—Trichlorbutylidene Glycol.—2,2,3-Trichlorbutan-1,1-diol.—A crystalline product obtained by the addition of water to liquid butyl chloral. The structural formulas of butylchloral hydrate and butyl chloral, respectively, are given below.

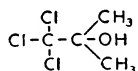


For tests and standards, see Section B.

*Actions and Uses.*—The action of this preparation is similar to that of chloral hydrate.

*Dosage.*—From 0.3 to 1.3 Gm.

**CHLOROBUTANOL-U. S. P.**—Chloretone-Parke, Davis.—“Chlorobutanol may be anhydrous or it may contain up to about one-half molecule of water.” *U. S. P.* Its structural formula is:



For description and standards see the *U. S. Pharmacopeia* under Chlorobutanol.

*Actions and Uses.*—Chlorobutanol is said to be absorbed unchanged from the alimentary tract, but to be decomposed in the body. It is a local anesthetic with an action weaker than that of cocaine, but sufficient action frequently to prevent vomiting from slight gastric irritation. Its antiseptic action is said to be fifteen times as strong as that of boric acid. It acts on the central nervous system similarly to chloral hydrate, and although the claim has been made that hypnotic doses are without effect on the circulation and respiration, independent observers have described a fall of blood pressure and interference with respiration in animals, and consider it fully as dangerous as chloral hydrate. In man 6.5 Gm. (100 grains) caused severe symptoms, but recovery occurred. It is said to be useful as a mild local

anesthetic in dentistry, etc., as a preservative for hypodermic solutions and for insomnia, vomiting and spasmodic conditions.

*Dosage.*—From 0.3 to 1.3 Gm., dry or in capsules. Hypodermically as a local anesthetic a saturated aqueous solution may be used.

MERCK & CO., INC.

**Chlorobutanol (*Hydrous Powder*):** Bulk. This product is used in the preparation of aqueous solutions.

**Chlorobutanol (*Anhydrous Powder*):** Bulk. This product is used in the preparation of oil solutions.

PARKE, DAVIS & COMPANY

**Chloretone (*Powder*):** Bulk.

**Boro-Chloretone (*Powder*):** A dusting powder composed of chloretone, 1 part; boric acid, 1 part; purified talc, 2 parts.

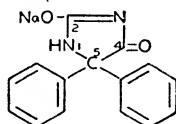
**Capsules Chloretone:** 0.2 Gm. and 0.3 Gm.

**Inhalant Chloretone:** Chlorobutanol, 1 Gm.; camphor, 2.5 Gm.; menthol, 1.8 Gm.; oil of cinnamon, 60 mg.; refined liquid petrolatum, 94.64 Gm.

U. S. trademark 175,422.

## Hydantoin Derivatives

**DIPHENYLHYDANTOIN SODIUM-U. S. P.**—Dilantin Sodium-Parke, Davis.—U. S. P.—5,5-Diphenylhydantoinate Sodium.—Phenytoin Sodium.—“When dried at 100 C. for 4 hours, contains not less than 90.5 per cent and not more than 92 per cent of diphenylhydantoin ( $C_{15}H_{12}N_2O_2$ ).” U. S. P. The formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Diphenylhydantoin Sodium and Diphenylhydantoin Sodium Capsules.

*Actions and Uses.*—Diphenylhydantoin sodium is an anticonvulsant with a relatively weak hypnotic action. It is used in the treatment of epileptic patients who are not benefited by phenobarbital or bromides and those in whom these drugs induce disagreeable side actions. Diphenylhydantoin sodium appears to be more effective in controlling seizures of the grand mal type

than in those of the *petit mal*. It does not cure congenital mental defects or the mental deterioration often observed in the epileptic. Various side actions of different degrees of severity which have been observed include dizziness, dry skin, dermatitis, rash, itching, tremors, fever, nausea, vomiting, blurred vision, fatigue, apathy, difficult breathing and swallowing, nervousness, mental confusion and active hallucinations, and hyperplasia of the gums suggestive of scurvy, though its use does not interfere with the utilization of vitamin C. Diphenylhydantoin sodium is strongly alkaline and it may give rise to gastric irritation.

*Dosage.*—The optimum dosage of diphenylhydantoin sodium must be determined by the daily observation of its effects by the physician. The influence of the drug on seizures and the appearance of any of the side actions enumerated must be a guide to the dosage. Mild symptoms do not necessarily require that the dosage be stopped. The beginning adult dose is 0.1 Gm. with at least half a glass of water three times daily. If necessary this dose may be increased gradually to 0.2 Gm. three times daily. Children above the age of 6 years may be given 0.1 Gm. three times daily for one week, after which it may be increased if necessary to 0.1 Gm. four times daily with at least half a glass of water to prevent gastric irritation due to the alkalinity. Diphenylhydantoin sodium is more rapidly effective if given before meals, but should it cause gastric irritation it should be given immediately after meals. Children under 4 years of age may start with 0.03 Gm. mixed with cream (to disguise the bitter taste and to prevent gastric irritation) twice a day. Obviously such doses require the most careful supervision. If this dose is borne without side actions the dosage may be increased to 0.03 Gm. three or four times a day. Every slight increase in dosage is made only after the physician is convinced that such increase is necessary and that no harm is to be anticipated.

The transition from phenobarbital, bromides or other hypnotic-type drugs to diphenylhydantoin sodium should be made gradually with some overlapping in dosage. By this procedure the danger of phenobarbital or bromide withdrawal symptoms (increased number of seizures) is minimized, and side actions incident to the beginning administration of diphenylhydantoin sodium are lessened.

AMERICAN PHARMACEUTICAL Co., INC.

**Capsules Diphenylhydantoin Sodium: 0.1 Gm.**

PARKE, DAVIS & COMPANY

**Kapseals Dilantin Sodium: 0.1 Gm. and 30 mg.**

U. S. trademark applied for.

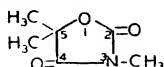
PREMO PHARMACEUTICAL LABORATORIES, INC.

**Diphenylhydantoin Sodium (Powder): 28 Gm., 113 Gm. and 453 Gm. bottles.**

**Capsules Diphenylhydantoin Sodium: 30 mg. and 0.1 Gm.**

## Oxazolidine Derivatives

**TRIMETHADIONE.** — **Tridione**—Abbott. — 3,5,5-Tri-methyloxazolidine-2,4-dione.—The structural formula of trimethadione may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Trimethadione is primarily an anticonvulsant and has only minor analgesic properties. It is used in the treatment of epilepsy, in which it is principally effective in cases with seizures of the true petit mal type. Its results in this condition appear to be somewhat better in children than in adults. It is ineffective in grand mal. It is also useful in psychomotor epileptic seizures, especially with diphenyl hydantoin sodium when the latter alone is ineffective. It may be tried in myoclonic and akinetic seizures of organic origin but is generally less effective than in the idiopathic forms of the disease. It has been used with diphenyl hydantoin sodium and/or phenobarbital in cases in which attacks are complicated by grand mal seizures. In some instances, the combination of drugs has served to increase the number of grand mal attacks as the petit mal has decreased and readjustment of dosage may be required for optimum therapeutic effect.

Toxic reactions to trimethadione appear to be relatively infrequent. Gastric irritation, nausea, skin eruptions, photosensitivity and blurring of vision with a diminution in visual acuity that is reversible may be encountered and are considered indications for temporary withdrawal or reduction in dosage of the drug. Photophobia appears to be less frequent in children than in adults. The skin manifestations that have been observed are not attributable to sensitization, and the visual disturbances have not been shown to be associated with optic nerve damage.

Rare cases in which aplastic anemia with a depression of all elements of the peripheral blood has occurred with the use of trimethadione indicate the need for repeated complete blood examinations in patients receiving this drug. It has been suggested that small initial doses be used and the patient cautioned to report at once any untoward symptoms that may ensue. Careful medical supervision of patients under treatment with trimethadione is essential. It should not be used in the presence of anemia, leukopenia or thrombocytopenia and employed with caution if at all in any type of blood dyscrasia.

It is contraindicated in patients with advanced renal or hepatic disease or with disease of the optic nerve.

**Dosage.**—In petit mal epilepsy, the dosage required may vary from 1 to 2 Gm. daily, given in divided doses of three to seven 0.3 Gm. capsules per day. In children under 6 years of age it

is advisable to begin with 0.15 to 0.3 Gm. three times daily and to increase this if necessary. Optimum dosage must be determined for each patient. Tablets of the drug are compounded with an appreciable amount of magnesium trisilicate as an absorbent. Such tablets are contraindicated in large quantities for children for whom a ketogenic diet has been prescribed.

**ABBOTT LABORATORIES**

**Capsules Tridione:** 0.3 Gm.

**Dulcet Tablets Tridione:** 0.15 Gm.

U. S. trademark 500,527.

**Solution Tridione:** 500 cc. and 4,000 cc. bottles.

U. S. trademark 500,401.

### Sulfonmethanes

Two analogous compounds formed by the substitution of sulfone radicals in methane have been applied in therapeutics. The first, sulfonmethane-N. F. (sulfonal) is diethylsulfon-dimethylmethane; the second, sulfonethylmethane-N. F. (trional) is diethylsulfonmethylethylmethane. The latter has been generally given the preference.

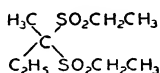
Sulfonmethane is soluble with difficulty and slowly absorbed and its hypnotic action is but slowly established; sulfonethylmethane is somewhat more soluble than sulfonal and acts more quickly. Both drugs are preferably given in hot liquids; and in the case of sulfonmethane, the hypnotic effect is likely to be postponed for several hours. Sometimes it is not developed until the following day. Sulfonethylmethane is usually effective in an hour or two.

The sulfonmethanes in therapeutic doses produce sleep without noticeable effect on the circulation or respiration. In larger doses, acute poisoning occurs, evidenced by disturbances of the digestive organs, the metabolism and the nervous system. When administered for too long a period, cumulation is likely to occur, producing a condition of chronic poisoning which terminates fatally in a large percentage of cases. In such cases, hematoporphyrin derived from hemoglobin turns the urine pink or red. This should serve as a warning, indicating the immediate withdrawal of the drug.

The symptoms of poisoning consist of persisting confusion, ataxia, constipation, vomiting, albuminuria and nephritis.

*Dosage.*—The usual dose of either sulfonmethane or sulfonethylmethane is 1.0 Gm. with a maximum of 2 Gm. for the first and 4 Gm. for the second. When these drugs are used frequently, the administration should be suspended once in two or three days to allow of complete elimination, and the urine should be examined frequently for hematoporphyrin.

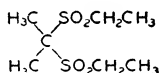
**SULFONETHYLMETHANE**—N. F.—Diethylsulfonmethylethylmethane.—The structural formula may be represented as follows:



For description and standards see The National Formulary under Sulfonethylmethane.

*Actions, Uses and Dosage.*—See general article, Sulfonmethanes.

**SULFONMETHANE**—N. F.—Sulfonal.—The structural formula may be represented as follows:

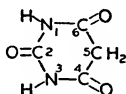


For description and standards see The National Formulary under Sulfonmethane.

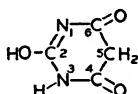
*Actions, Uses and Dosage.*—See general article, Sulfonmethanes.

## Barbituric Acid Derivatives

Barbituric acid is a cyclic compound obtained by the combination of urea and malonic acid, and is also called malonyl urea:



It may exist in the "keto" form represented above, or in the "enol" form shown below. The latter form is derived by the migration of a hydrogen atom from the nitrogen atom in position 1 (or 3) to the oxygen attached to the carbon in position 2.



This form is acidic in nature, the migrant H atom ionizing to produce a hydrogen ion and a barbiturate ion, and allows the formation of metallic salts.



Barbituric acid itself does not possess hypnotic properties. These are conferred when the hydrogens on carbon in the 5-position are replaced by organic groups. Most of the clinically useful barbiturates have aliphatic radicals substituting for the hydrogen atoms; a few have alicyclic radicals. Phenobarbital is the only important barbiturate which contains an aromatic radical. Other variations in structure include the substitution of halogen for one of the hydrogens attached to the carbon in the 5-position, the substitution of an organic radical for the hydrogen attached to either of the nitrogens, and the replacement of oxygen attached to the carbon in the 2-position with sulfur to form a thiobarbiturate.

The following compounds and their salts are described in N. N. R.:

DURATION OF ACTION	COMPOUNDS	SUBSTITUENTS		
		R <sub>1</sub>	R <sub>2</sub>	Other
Long	Barbital	Ethyl	Ethyl	
Long	Phenobarbital	Ethyl	Phenyl	
Intermediate	Alurate	Allyl	Isopropyl	
Intermediate	Butisol Sodium	Ethyl	1-Methylpropyl	
Intermediate	Delvinal	Ethyl	1-Methyl-1-butenyl	
Intermediate	Dial	Allyl	Allyl	
Intermediate	Ipral	Ethyl	Isopropyl	
Intermediate	Neonal	Ethyl	n-Butyl	
Short	Amytal	Ethyl	Isoamyl	
Short	Nostal	$\beta$ -Bromallyl	Isopropyl	
Short	Ortal	Ethyl	n-Hexyl	
Short	Pentobarbital	Ethyl	1-Methylbutyl	
Short	Pernoston	$\beta$ -Bromallyl	Butyl	
Short	Phanodorn	Ethyl	Cyclohexenyl	
Short	Sandoptal	Allyl	Isobutyl	
Short	Seconal	Allyl	1-Methylbutyl	
Ultrashort	Evipal	Methyl	Cyclohexenyl	1-Methyl
Ultrashort	Pentothal	Ethyl	1-Methylbutyl	2-Thio

*Actions and Uses.*—The derivatives of barbituric acid are effective sedatives and hypnotics, and are used as such in insomnia, hysteria, neurasthenia, thyroid disease, chorea, mental disturbances and epilepsy. They are used in combination with the analgesic drugs for the relief of pain, although they are not analgesic in themselves. Other specialized uses of the barbiturates include general anesthesia and basal narcosis, premedication before surgical operations, the control of pain in labor, psychiatric treatment, and the prevention and treatment of convulsions. These uses will be discussed individually. The therapeutic effects are exerted on the higher centers of the brain, and therapeutic doses do not usually cause any apparent injury to the vital organs.

The barbiturates are often classified according to their duration of action, as long, intermediate, short, and ultra-short-acting drugs. In general, the interval between the administration of the drug and the exhibition of its therapeutic effect corresponds to this classification; i.e., the short-acting drugs take effect rapidly, the long-acting drugs take effect slowly.

For prolonged mild sedation in such conditions as neurasthenia and thyroid disease, and to reduce the frequency of epileptic convulsions, small doses of a long-acting barbiturate are useful. The effects of the individual doses overlap and produce a rather evenly maintained sedation.

Simple insomnia can be divided into two categories: one in which there is difficulty in falling asleep, but once sleep is achieved, it is undisturbed; the other in which sleep comes easily but is disturbed by nocturnal or very early morning awakening. For insomnia of the first type the drug of choice is a short-acting barbiturate, which produces sleep within one-half hour, and whose effect disappears within four to six hours. For the second type of insomnia, the drug of choice is an intermediate-acting barbiturate, whose effect comes on later and lasts six or eight hours. The sleep induced by small doses of these drugs closely resembles natural sleep, and the patient generally awakens refreshed.

There is a fairly wide margin between the therapeutic and toxic doses of barbiturates now in clinical use. Occasionally, however, even after moderate doses, lassitude, vertigo, headache, nausea and diarrhea may occur. In some patients the barbiturates produce restlessness and excitement, and the use of these drugs is contraindicated in such patients. Excitement and restlessness are prone to occur when the barbiturates are administered to patients in severe pain. The mechanism of action in this instance is that the drug does not relieve the pain but depresses the higher centers which normally act as inhibitors. Fairly typical skin eruptions are sometimes observed, especially after prolonged administration. Long continued use may result in addiction.

The long-acting barbiturates are largely excreted by the kidney: the short-acting barbiturates are destroyed to a large extent in the liver. The fate of pentothal in the body has been a matter of controversy but recent evidence indicates that it, too, is destroyed in the liver. The slower the excretion or destruction of the various members of this group, the more lasting is the action. With very slow excretion, prolonged administration of ordinary doses may result in cumulative toxic effects. This must be borne in mind especially when the drugs are administered to patients with damaged liver or kidneys.

Poisoning with the barbiturates is a rather common occurrence, both accidentally and with suicidal intent. The toxic effects of overdosage are respiratory depression, peripheral vascular collapse, feeble heart beat, lowered body temperature, and long-continued stupor with depressed or absent reflexes. Death results from depression or paralysis of the respiration, or from pulmonary complications.

In the treatment of barbiturate poisoning the provision of adequate oxygenation is of primary importance. If there is complete respiratory paralysis, artificial respiration should be instituted at once, either manually or with a respirator or resusci-

tator. The use of oxygen is desirable both during artificial respiration and during the phase of depressed breathing. The cardiovascular system should be supported by intravenous infusions of saline or glucose solutions, care being taken, however, not to overload the heart. Occasionally the transfusion of whole blood may be desirable. The patient should be kept warm, and his position should be changed frequently in order to prevent the onset of hypostatic pneumonia. Analeptic drugs may be administered intravenously in divided doses when there is deep coma and severe respiratory depression. These should be given until the respiration improves and the corneal reflex returns.

The barbiturates are commonly used for pre-anesthetic medication, either alone or in combination with other drugs. A short or intermediate-acting drug is administered on the evening before operation to reduce apprehension and provide a restful sleep. From one to two hours before operation a short-acting barbiturate is administered, often with morphine and atropine. The barbiturates are particularly valuable for pre-medication when a local or regional anesthetic is to be administered, since they reduce the frequency and severity of toxic reactions to the local anesthetic drugs.

Barbiturates are valuable in the treatment of convulsions resulting from local anesthetic drugs as well as in the treatment of convulsions from most other causes. The cautious intravenous administration of a short or ultrashort-acting barbiturate is usually very satisfactory in stopping a severe convulsion. For long continued control of convulsions, as in tetanus, the drugs may be given rectally as described below under basal narcosis.

The barbiturates are useful in controlling excitement and manic states. Prolonged sleep induced by the barbiturates has been found useful in the treatment of psychic casualties of warfare. The intravenous barbiturates have also been found useful in the procedure of narco-analysis. A psychiatric interview is conducted while the patient is in a semiconscious state produced by small doses of drug. Therapy of some mental disorders is rendered easier by this procedure.

The barbiturates are also used in the control of pain during labor, either alone, or in combination with scopolamine to produce a form of twilight sleep. A frequent complication in this procedure is delirium and excitement of the mother, caused by pain which the barbiturates do not relieve. Amnesia may be achieved with moderate doses. The newborn infant is also affected by the drug given to the mother. In any large series of cases there is an increase in the incidence of delayed respiration, and more of the infants require resuscitation. The harmful effects upon the infant should be remembered by all who use this method, and care should be taken to avoid excessive dosage.

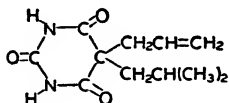
The ultrashort-acting drugs are used as intravenous anesthetics. They should be administered only by those trained in

anesthesia because serious or fatal complications may occur even during a minor procedure. The drugs should be administered in a 2.5 per cent solution or less, to avoid the possibility of venous thrombosis. Induction is rapid and pleasant. Respiratory depression and apnoea are serious complications which may occur. The anesthetist must be capable of treating these and must have equipment at hand to give artificial respiration with oxygen. Laryngospasm and vomiting may occur but are not frequent. These drugs are contraindicated in shock or in operative procedures where shock may be expected. They are also contraindicated in patients with diminished pulmonary ventilation or respiratory obstruction, and in operations about the mouth and nose which may cause blood to run down the respiratory tract. Muscular relaxation with these drugs is poor, and attempts to increase the relaxation result in overdosage.

The intravenous barbiturates are of value for induction of anesthesia and for short operations which do not require muscular relaxation. Oxygen should be given during the procedure. Mixtures of 50 per cent nitrous oxide and oxygen may advantageously be administered to improve the anesthesia and reduce the amount of barbiturate used. Curare may be given to produce muscular relaxation during barbiturate anesthesia. The intravenous barbiturates are deceptively easy to administer, and caution must be exercised to prevent the occurrence of a catastrophe.

Basal narcosis may be produced by the rectal administration of short or ultrashort-acting barbiturates. The drug is dissolved in a small volume of warm tap water and administered as a retention enema. Sleep is produced in about ten minutes. Short minor operative procedures may be performed without further anesthesia, but for most operations the basal narcosis must be supplemented with one of the other anesthetic drugs. This method is particularly valuable for quiet induction of anesthesia in apprehensive children and in toxic thyroid patients. Pentothal sodium may be used in this manner in a dosage of 20 mg. per pound (450 Gm.) of body weight, the total dose not to exceed 3 Gm. Prolonged convulsive states, as in tetanus, may be controlled in this manner with reduced dosage. The precautions necessary with this method are the same as those applying in intravenous barbiturate anesthesia.

**ALLYL BARBITURIC ACID.**—Sandoptal-Sandoz.—5-Isobutyl-5-allyl barbituric acid.—5-Isobutyl-5-allyl malonyl-urea. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The same as those of barbitol and its therapeutically useful derivatives.

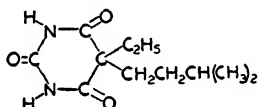
**Dosage.**—For mild insomnia, 0.2 Gm., for use in obstinate cases of insomnia, 0.4 to 0.8 Gm.

SANDOZ CHEMICAL WORKS, INC.

**Tablets Sandoptal:** 0.2 Gm.

U. S. trademark 284,623.

**AMOBARBITAL Amytal-Lilly.**—5-Isoamyl-5-ethylbarbituric acid.—Isoamylethylmalonylurea. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses of amobarbital resemble those of barbitol. It is used as a sedative and hypnotic in the control of insomnia and as a preliminary to surgical anesthesia.

**Dosage.**—It is given orally in tablet form with water or hot milk. As a sedative: 20 mg. to 40 mg. two or three times daily. As a hypnotic: 0.1 to 0.3 Gm. one-half to one hour before sleep is desired. For use before local or general anesthesia the dosage ranges between 0.2 and 0.6 Gm., being determined by a large number of factors (age, etc.). It can be used safely for such purposes only by those who have had much experience and are familiar with the literature concerning such use. As an antispasmodic in tetanus, 0.4 to 0.8 Gm. may be required to control convulsions.

ELI LILLY AND COMPANY

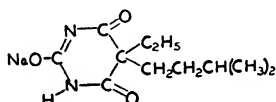
**Amytal (Powder):** Bulk.

**Elixir Amytal:** 0.44 Gm. per 100 cc. and 0.88 Gm. per 100 cc. in a vehicle containing methenamine 0.416 Gm. and 0.83 Gm. per 100 cc. respectively, alcohol, propylene glycol, water and aromatics; methenamine is present for the purpose of increasing the solubility of the amobarbital.

**Tablets Amytal:** 8 mg., 16 mg., 32 mg., 48 mg. and 96 mg.

U. S. patent 1,514,573 (Nov. 4, 1924; expired). U. S. trademark 161,125.

**AMOBARBITAL SODIUM.**—Amytal Sodium-Lilly.—Sodium Isoamylethylbarbiturate.—The monosodium salt of 5-isoamyl-5-ethylbarbituric acid. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses of amobarbital sodium resemble those of barbitol. The product is used as a sedative and hypnotic in the control of insomnia and as a preliminary to surgical anesthesia.

**Dosage.**—As a potent sedative or hypnotic 65 mg. to 0.5 Gm., repeated if necessary at intervals of six hours. For use before local or general anesthesia the dosage ranges between 0.2 and 0.6 Gm. being determined by a large number of factors (age, etc.). As an antispasmodic in tetanus, from 0.4 to 0.8 Gm. may be required to control convulsions. It can be used safely for such purposes only by those who have had much experience and are familiar with the literature concerning such use. In some patients barbitol derivatives produce restlessness and excitement, and to these patients amobarbital sodium should not be administered. It may be administered by mouth, or, if necessary, the same dose may be given rectally, in the form of capsules inserted as suppositories or as powder placed in a little water; it should be administered intravenously only in those conditions outlined in the general section on barbituric acid derivatives. The maximum single dose of 1 Gm. should not be used except when an intense and prolonged effect is desired. Usually no more than 1 Gm. will be necessary in a 24-hour period.

ELI LILLY AND COMPANY

**Amytal Sodium (Powder):** 30 cc.

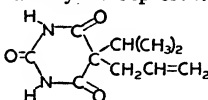
**Pulvules Amytal Sodium:** 0.2 Gm. and 0.1 Gm.

**Amytal Sodium:** 65 mg., 0.125 Gm., 0.25 Gm., 0.5 Gm. and 1.0 Gm. ampuls. Each ampul of 0.25 Gm., 0.5 Gm. and 1.0 Gm. is accompanied by an ampul of distilled water.

**Suppositories Amytal Sodium:** 0.2 Gm.

U. S. patent 1,514,573 (Nov. 4, 1924; expired). U. S. trademark 161,125.

**APROBARBITAL.**—Alurate-Hoffmann-LaRoche.—5-Allyl-5-isopropylbarbituric acid. — Allylisopropyl-malonylurea. The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—The actions and uses of aprobarbital are essentially similar to those of barbital, but aprobarbital is more active than barbital and is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as a hypnotic.

*Dosage.*—For mild cases of insomnia, 65 mg. may be administered at bedtime. In obstinate cases, 0.13 Gm. may be given.

HOFFMANN-LA ROCHE, INC.

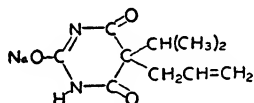
**Alurate (Powder):** Bulk.

**Elixir Alurate:** Contains aprobarbital approximately 0.9 Gm. per hundred cubic centimeters in a palatable elixir containing alcohol, 20 per cent.

U. S. patent 1,444,802 (Feb. 13, 1923; expired). U. S. trademark 230,059.

**Tablets Alurate:** 65 mg.

**APROBARBITAL SODIUM.**—Alurate Sodium-Hoffmann-La Roche.—Sodium 5-allyl-5-isopropyl barbiturate. The monosodium salt of 5-allyl-5-isopropyl malonylurea. Its structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—The same as those for aprobarbital. The soluble sodium salt is intended for oral or rectal administration, particularly as pre-anesthesia medication. Aprobarbital sodium also be used in other cases in which large individual doses are required.

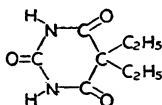
*Dosage.*—The average preoperative dose is 10 mg. per kilogram of body weight. One third of the calculated dose is given ten or twelve hours prior to operation (usually the evening before); the remainder, two hours before operation. Experience is necessary in the use of these large dosages, as the amount of the drug must be adjusted to the individual patient in order to avoid undesirable reactions.

HOFFMANN-LA ROCHE, INC.

**Capsules Alurate Sodium:** .227 Gm. Each capsule is equivalent to approximately 0.2 Gm. of aprobarbital.

U. S. patent 1,444,802 (Feb. 13, 1923; expired). U. S. trademark 230,059.

**BARBITAL-U. S. P.—Veronal-Winthrop-Stearns.**—Diethylbarbituric Acid.—Barbitone.—Diethylmalonylurea. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Barbital and Barbital Tablets and The National Formulary under Barbital Elixir.

*Actions and Uses.*—See the general article, Barbituric Acid Derivatives. Barbital is quickly absorbed, especially when it is given in solution. Small doses induce sleep, apparently with little other effect, and are relatively safe; but fatalities have followed its indiscriminate use.

*Dosage.*—As hypnotic, 0.3 Gm., best prescribed in the form of powder to be given in hot fluid, such as hot milk, half an hour or an hour before bedtime. Pills or tablets should be crushed before swallowing, to insure absorption. From 0.1 to 0.15 Gm. are used with analgetics for the relief of pain.

ABBOTT LABORATORIES

**Tablets Barbital:** 0.3 Gm.

MALLINCKRODT CHEMICAL WORKS

**Barbital (Powder):** bulk.

MERCK & Co., INC.

**Barbital (Powder):** bulk.

**Tablets Barbital:** 0.3 Gm.

WINTHROP-STEARNs, INC.

**Veronal (Powder):** bulk.

**Elixir Veronal:** Each 4 cc. contains barbital 0.13 Gm. in a menstruum containing alcohol 33.5 per cent.

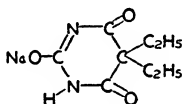
**Tablets Veronal:** 0.3 Gm.

U. S. patent 782,739 (Feb. 14, 1905; expired). U. S. trademark 40,115.

**BARBITAL SODIUM-U. S. P.—Medinal-Schering & Glatz, Division of Wm. R. Warner & Co., Inc.**—Soluble barbital.—Sodium diethylbarbiturate.—Soluble barbitone.—Sodium diethylmalonylurea.—U. S. P.—“Contains not less than 88 per cent and not more than 90 per cent of  $C_8H_{12}N_2O_3$  [barbital] calculated on a moisture-free basis, corresponding to not



less than 98.5 per cent of  $C_8H_{11}N_2O_3Na$ ." U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Barbitol Sodium and Barbitol Sodium Tablets.

**Actions and Uses.**—The same as those of barbitol. It is claimed, however, that this drug acts more rapidly on account of its greater solubility. Because of its solubility, administration by rectal injection and also subcutaneous injection has been proposed.

**Dosage.**—The same as that of barbitol. It should be administered in aqueous solution.

ABBOTT LABORATORIES

Tablets Barbitol Sodium: 0.3 Gm.

MERCK & Co., INC.

Barbitol Sodium (*Powder*): bulk.

Tablets Barbitol Sodium: 0.3 Gm.

SCHERING & GLATZ, DIVISION OF WM. R. WARNER & Co., INC.

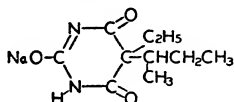
Medinal (*Powder*): 30 Gm. bottles.

**Elixir Medinal:** 180 cc. and 3.79 liters. A solution containing in each 4 cc., 0.12 Gm. medinal in 20 per cent alcohol.

Tablets Medinal: 0.3 Gm.

U. S. patents 780,241 (Jan. 17, 1905; expired) and 879,499 (Feb. 19, 1908; expired). U. S. trademark 269,753.

**BUTABARBITAL SODIUM.**—Butisol Sodium-McNeil.—Sodium 5-ethyl-5-*sec.*-butyl barbituric acid.—Sodium 5-ethyl-5(1-methylpropyl)barbiturate. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Butabarbital sodium produces pharmacologic actions similar to other barbiturates. With average doses the rapidity and duration of its action is intermediate between the fast-acting derivative, pentobarbital, and the longer-acting

barbital and phenobarbital. Following oral administration the drug usually exerts initial effects within 30 minutes. Sedation is sustained for approximately five to six hours. It is thus suited for the production of a relatively mild and more continuous depression than can be obtained with the shorter-acting barbiturates, yet its action is less prolonged than with barbital or phenobarbital.

Butabarbital sodium is destroyed fairly rapidly in the body, probably in the liver. It is not excreted as such in the urine except with excessive doses and therefore is not contraindicated in the presence of renal disease. Experimental studies indicate it to be essentially nontoxic for the liver. Its therapeutic coefficient is approximately equal to that of pentobarbital and greater than that of phenobarbital.

Butabarbital sodium is used orally as a simple sedative or hypnotic and for pre-operative sedation and obstetric hypnosis. Essentially the same clinical precautions to avoid side effects should be observed as for other barbiturates.

*Dosage.*—Orally: sedative, 8 to 60 mg.; hypnotic, 45 mg. to 0.2 Gm., depending on the purpose and the patient. In general the duration of action is dependent on the size of the dose and the size of the patient. The average oral adult sedative dose is 30 mg.; the average hypnotic dose, 0.1 Gm.

MCNEIL LABORATORIES, INC.

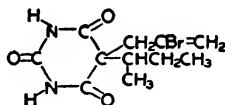
**Capsules Butisol Sodium:** 0.1 Gm.

**Elixir Butisol Sodium:** 0.2 Gm. per 30 cc. Butisol Sodium dissolved in a flavored elixir containing 7 per cent alcohol.

**Tablets Butisol Sodium:** 15 mg. and 50 mg.

U. S. trademark 378,610.

**BUTALLYLONAL.** — **Pernoston-Ames.** — 5-*sec.*-butyl-5- $\beta$ -bromallyl barbituric acid.—5-(butyl-2)-5- $\beta$ -brompropenyl malonylurea. The structural formula may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—The actions and uses of butallylonal are essentially similar to those of barbital, but butallylonal is more active than barbital and is used in correspondingly smaller doses. It is promptly absorbed and is rapidly changed and destroyed within the body. It is used in combating insomnia due to emotional strain and nervous instability.

**Dosage.**—One tablet (194 mg.) given one-half hour before sleep is desired, preferably followed by a glass of warm milk or lemonade. For hypnosis in the presence of pain: one tablet given in conjunction with acetylsalicylic acid.

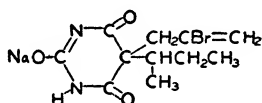
AMES COMPANY, INC.

**Pernoston (Powder):** Bulk.

**Tablets Pernoston:** 194 mg.

U. S. patent 1,739,662 (Dec. 17, 1929; expired 1946). U. S. trademark 330,845.

**BUTALLYLONAL SODIUM.** — **Pernoston Sodium-Ames.**—Sodium 5-*sec.*-butyl-5- $\beta$ -bromallylbarbiturate.—Sodium 5-(butyl-2)-5- $\beta$ -brompropenylmalonylurea. The sodium salt of butallylonal. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The action of butallylonal sodium is like that of pernoston except that the effects are induced almost immediately after its intravenous injection. It is used when the oral administration of a barbiturate is not feasible either because of interference with swallowing and when prompt action is imperative, as in the presence of convulsions. The effects are delayed for from 30 to 45 minutes after the intramuscular injection. The intravenous use demands the rigid observance of the proper technic. The contraindications are important. Besides those that apply to all barbiturates, these contraindications include congestive heart failure, anoxia as the result of pulmonary disease, asphyxia from the inhalation of gases, profound anemia and respiratory disturbances resulting from diseases of the central nervous system. Butallylonal sodium should be administered extremely cautiously in the presence of marked hyper- or hypotension, in advanced general arteriosclerosis, to elderly or senile patients, and to patients who are emaciated from long standing chronic diseases.

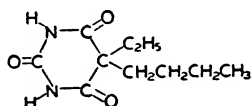
**Dosage.**—One cc. of the 10 per cent solution (in ampuls) per 12.5 Kg. of body weight injected intravenously at the rate of 1 cc. total per minute until the patient sleeps or until the full dose has been injected. The intramuscular dose is the same as that by vein, but it may be injected at once. Ampuls containing a deposit should not be used.

AMES COMPANY, INC.

**Solution Pernoston Sodium, 10%:** 2 cc. ampuls.

U. S. patent 1,739,662 (Dec. 17, 1929; expires 1946). U. S. trademark 330,845.

**BUTETHAL.** — **Neonal-Abbott.** — 5-*n*-Butyl-5-ethylbarbituric acid. — 5-*n*-butyl-5-ethylmalonylurea. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses of butethal are essentially similar to those of barbital, but it is about three times as active as the latter; hence it is used in correspondingly smaller doses. It is claimed that it exerts a sedative action to an exceptional degree, and that it is useful therefore in high nervous tension, neuroses and other conditions in which a sedative is required.

**Dosage.**—From 50 mg. to 0.4 Gm. For mild insomnias 50 mg. to 0.1 Gm. is stated ordinarily to produce sleep. A dose of 0.4 Gm. is the maximum dose which should be required in the course of twenty-four hours, administered in divided doses.

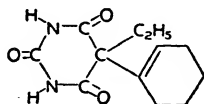
ABBOTT LABORATORIES

**Neonal (Powder):** Bulk.

**Tablets Neonal:** 0.1 Gm.

U. S. patent 1,609,520 (Dec. 7, 1926; expired). U. S. trademark 175,580.

**CYCLOBARBITAL.**—**Phanodorn-Winthrop-Stearns.** — Cyclohexenylethyl barbituric acid.—5- $\Delta^1$ -cyclohexenyl-5-ethylmalonylurea. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses of cyclobarbital resemble those of barbital. It is eliminated more rapidly than barbital; hence the action is not so lasting. This is an advantage when it is used merely to put one to sleep and sleep will

then continue without its further action. It is used mainly for its sedative action in neurasthenia, psychoses, and various types of insomnia.

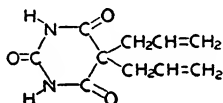
**Dosage.**—For the mildest type of simple insomnia, 0.1 Gm. or  $\frac{1}{2}$  tablet. In intractable or obstinate insomnia, from 0.2 to 0.4 Gm. or one to two tablets. The larger dose should not be repeated within less than twelve hours. The average dose is 0.2 Gm. or one tablet.

WINTHROP-STEARNs, INC.

Tablets Phanodorn: 0.2 Gm.

U. S. patent 1,690,796 (Nov. 6, 1928; expired).

**DIALLYL BARBITURIC ACID.**—Dial-Ciba.—5,5-Diallylbarbituric acid.—Diallylmalonylurea. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses of diallyl barbituric acid are essentially similar to those of barbital, but diallyl barbituric acid is more active than barbital and it is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as a hypnotic. Therapeutic doses act on the higher centers of the brain and exert no injurious action on respiration or circulation. The hypnotic action is induced within from one-half to one hour.

The actions and uses of diallyl barbituric acid with urethane are the same as those of diallyl barbituric acid; it is claimed that the ethyl carbamate and monoethylurea are used as solvents, and, in the amounts present, do not greatly affect the action of the diallyl barbituric acid content. Solution diallyl barbituric acid with urethane is proposed for intramuscular administration and, in the case of a pressing emergency only, for intravenous injection. The solution being strongly hypertonic, subcutaneous injection should never be employed.

**Dosage.**—As a sedative: 30 mg. three or four times daily. As a hypnotic: 0.1 to 0.3 Gm. one-half to one hour before sleep is desired.

CIBA PHARMACEUTICAL PRODUCTS, INC.

**Dial (Powder):** 10 Gm. and 30 Gm.

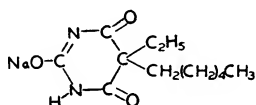
**Elixir Dial:** Each 4 cc. contains 50 mg. in a menstruum containing alcohol 25 per cent.

**Solution Dial with Urethane:** 1 cc. and 2 cc. ampuls. Each cubic centimeter contains Dial 0.1 Gm. ethyl carbamate (urethane) 0.4 Gm., monoethylurea 0.4 Gm. and water q. s.

**Tablets Dial:** 30 mg. and 0.1 Gm.

U. S. patent 1,042,265 (Oct. 22, 1912; expired). U. S. trademark 98,204 and 126,088.

**HEXETHAL SODIUM.**—Ortal Sodium-Parke, Davis.—Sodium 5-*n*-hexyl-5-ethyl barbiturate.—Sodium *n*-hexylethyl malonylurea.—The monosodium salt of 5-*n*-hexyl-5-ethyl barbituric acid. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses of hexethal sodium are essentially similar to those of barbital, but hexethal sodium is more active than barbital and it is used in correspondingly smaller doses.

**Dosage.**—From 0.2 to 0.4 Gm. followed by a glass of water. It is rarely necessary to give more than 1 Gm. in 24 hours. When oral administration is contraindicated, hexethal sodium may be administered rectally.

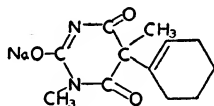
**Caution:** *Aqueous solutions of hexethal sodium are not stable but decompose on standing; on boiling, precipitation occurs with evolution of ammonia.*

PARKE, DAVIS & COMPANY

**Capsules Oral Sodium:** 50 mg., 0.2 Gm., 0.3 Gm.

U. S. patent 1,624,546 (April 12, 1927; expired). U. S. trademark 302,616.

**HEXOBARBITAL SOLUBLE.**—Evipal Sodium-Winthrop-Stearns.—Evipal Soluble-Winthrop-Stearns.—Sodium N-methylcyclohexenylmethylbarbiturate.—The sodium salt of 1,5-dimethyl-5- $\Delta^1$ -cyclohexenyl barbituric acid. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses of hexobarbital soluble are essentially similar to those of pentobarbital sodium except

that it is designed only for intravenous use to produce anesthesia of short duration. When injected intravenously it is a quick-acting, general anesthetic with an early recovery period. In the majority of cases consciousness is restored in from fifteen to thirty minutes, depending on the amount of drug injected. Not uncommonly there follows some drowsiness or sleep if the patient is left undisturbed. While the intravenous use of barbiturates is a valuable procedure under certain circumstances it should be undertaken only by those experienced in this field. It should not be looked on as a routine office procedure; adequate facilities should be at hand to combat untoward reactions. Ataxia and transient amnesia may occasionally be encountered. Contraindications are in general those of the barbital compounds and general anesthetics.

**Dosage.**—As there is considerable variation in individual reactivity to any of the barbiturates, the dose must be individualized. In general, 2 cc. to 4 cc. of a 10 per cent solution is required to induce unconsciousness in adults; this is injected intravenously at the rate of 1 cc. per ten seconds. An additional 1 cc. or 2 cc. may be necessary if relaxation is not obtained with the initial dose, or it may be required during the operative procedure. A total amount of 10 cc. of this 10 per cent solution is seldom required for adults, and it cannot be exceeded without danger.

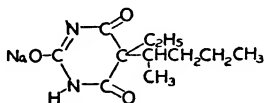
**Caution:** *If the solution is discolored or shows the presence of undissolved particles, even though it is freshly prepared, it should be discarded. The powder and solution undergo change on exposure to air and should not be kept for future use.*

WINTHROP-STEARNs, INC.

**Evipal Soluble:** 0.5 Gm. and 1 Gm. powder in ampuls, packaged with or without sterile distilled water.

U. S. patent 1,947,944. U. S. trademark 315,515.

**PENTOBARBITAL SODIUM-U. S. P.**—Soluble Pentobarbital. "Contains not less than 90 per cent and not more than 92 per cent of pentobarbital ( $C_{11}H_{18}N_2O_3$ ), calculated on a moisture-free basis corresponding to not less than 98.8 per cent of  $C_{11}H_{17}N_2O_3Na$ ." U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Pentobarbital Sodium, Pentobarbital Sodium Capsules and Pentobarbital Sodium Tablets and The National Formulary under Pentobarbital Elixir.

**Actions and Uses.**—The actions and uses of pentobarbital sodium are essentially similar to those of barbital, but it is

effective in smaller doses. It may be administered by mouth and rectum and may be injected intravenously (see general article on barbituric acid derivatives). The action is of relatively brief duration, which may constitute an advantage, especially when relatively large doses are administered. It may be administered intravenously for the control of convulsive seizures due to acute cocaine and procaine poisoning, chorea, eclampsia, meningitis, picrotoxin poisoning, strychnine poisoning, rabies and tetanus, and in the treatment of certain psychoses. It is used as a sedative, particularly prior to local, general or spinal anesthesia. It can be used safely for such purposes only by those who have had adequate experience and who are familiar with the literature concerning such use.

**Dosage.**—Orally, as hypnotic, 0.1 Gm.; as preanesthetic sedative, 0.2 Gm. Rectally, for analgesia: for infants up to 1 year, 30 mg., up to 3 years, 60 mg.; for adults, 0.32 to 0.38 Gm. dissolved in a few cubic centimeters of water. Average intravenous dose for adults has been 0.2 to 0.3 Gm. with 0.5 Gm. as maximum dose; for children has not been definitely decided, although a child 6 to 12 years may receive up to 0.1 to 0.2 Gm.

**Caution:** *Aqueous solutions of pentobarbital sodium are not stable but decompose on standing; on boiling, a precipitation occurs with evolution of ammonia.*

LAKESIDE LABORATORIES, INC.

**Solution Pentobarbital Sodium and Benzyl Alcohol:** 1 cc. and 2 cc. ampuls. Each cubic centimeter contains 0.162 Gm. of pentobarbital sodium and 20 mg. of benzyl alcohol dissolved in propylene glycol.

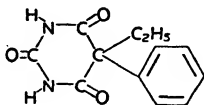
ELI LILLY & COMPANY

**Pentobarbital-Sodium:** 0.5 Gm., marketed in ampuls with or without a 10 cc. size ampul of distilled water.

PREMO PHARMACEUTICAL LABORATORIES, INC.

**Solution Pentobarbital Sodium:** 1 cc. and 2 cc. ampuls. Each cubic centimeter contains pentobarbital sodium 0.1625 Gm. and benzyl alcohol 2 per cent; in propylene glycol.

**PHENOBARBITAL-U. S. P. — Luminal-Winthrop-Stearns.** — Phenylethylmalonylurea. — Phenobarbitone. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Phenobarbital, Phenobarbital Tablets, and Phenobarbital Elixir.



**Actions and Uses.**—The introduction of the phenyl group increases the hypnotic and sedative action of phenobarbital over that of barbitol. The toxicity appears to be increased in about the same ratio. The sleep may be preceded by a period of excitement. Moderately large therapeutic doses sometimes cause severe circulatory depression. Habit formation has been reported.

Phenobarbital has a sedative action on respiration, lessening the frequency of breathing. It is eliminated by the kidneys, a certain portion being probably decomposed in the organism. No gastric disturbances have been observed.

Phenobarbital is used as a useful hypnotic in nervous insomnia and conditions of excitement of the nervous system; its chief use in this field is as a sedative, and as an antispasmodic in the treatment of epilepsy, in which it lessens the frequency and severity of seizures. Its use as a sedative has also been proposed in chorea, neurasthenia, cardiac and gastric neuroses, climacteric disorders, dysmenorrhea, exophthalmic goiter, and preoperative and postoperative cases.

**Dosage.**—From 15 mg. to 0.2 Gm. increased if necessary to 0.6 Gm. The average dose is 0.1 Gm. A maximum dose of 0.6 Gm. should not be exceeded.

**ABBOTT LABORATORIES**

**Phenobarbital (Powder):** Bulk.

**Tablets Phenobarbital:** 16 mg., 32.5 mg., 0.1 Gm.

**AMERICAN PHARMACEUTICAL COMPANY, INC.**

**Tablets Phenobarbital:** 32 mg., 16 mg. and 0.1 Gm.

**GEORGE A. BREON & COMPANY, INC.**

**Tablets Phenobarbital:** 32.4 mg. and 109 mg.

**BUFFINGTON'S INC.**

**Compressed Tablets Phenobarbital:** 16 mg., 32 mg. and 0.1 Gm.

**FLINT, EATON & COMPANY**

**Tablets Phenobarbital (White and Green):** 16 mg., 32 mg. and 0.1 Gm.

**GANE AND INGRAM, INC.**

**Phenobarbital (Powder):** Bulk.

**THE HARROWER LABORATORY, INC.**

**Tablets Phenobarbital:** 32 mg.

**MERCK & Co., INC.**

**Phenobarbital (Powder):** Bulk.

## THE WM. S. MERRELL COMPANY

**Solution Phenobarbital Sodium with Benzyl Alcohol 2% in Propylene Glycol 70%:** 0.12 Gm. and 0.3 Gm., 2 cc. ampuls.

**Tablets Phenobarbital:** 16 mg., 32.5 mg., 0.1 Gm.

## E. S. MILLER LABORATORIES, INC.

**Tablets Phenobarbital:** 15 mg., 30 mg. and 100 mg.

## SMITH-DORSEY COMPANY

**Tablets Phenobarbital:** 8 mg., 16 mg., 32.5 mg. and 0.1 Gm.

## THE UPJOHN COMPANY

**Tablets Phenobarbital:** 16 mg., 32.5 mg., 0.1 Gm. Supplied in both white and green tablets.

## THE VALE CHEMICAL CO., INC.

**Tablets Phenobarbital:** 16 mg., 32 mg. and 0.1 Gm.

## WARREN-TEED PRODUCTS COMPANY

**Solution Phenobarbital Sodium with Benzyl Alcohol 2% in Propylene Glycol:** 0.12 Gm. per cc., 1 cc. ampuls.

**Tablets Phenobarbital:** 16 mg., 32.5 mg., 0.1 Gm.

## WINTHROP-STEARNs, INC.

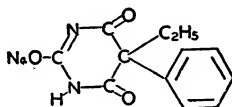
**Luminal (Powder):** Bulk.

**Elixir Luminal:** Each 4 cc. contains 16.2 mg. in a menstruum containing alcohol 26 per cent.

**Tablets Luminal:** 16.2 mg., 32.4 mg. and 109 mg.

U. S. patent 1,025,872 (May 7, 1912; expired). U. S. trademark 87,327.

**PHENOBARBITAL SODIUM-U. S. P.—Luminal Sodium-Winthrop-Stearns.**—Soluble phenobarbital, Soluble phenobarbitone.—“Contains not less than 89 per cent and not more than 91.5 per cent of phenobarbital ( $C_{12}H_{12}N_2O_3$ ), calculated on a moisture-free basis corresponding to not less than 98.5 per cent of  $C_{12}H_{11}N_2O_3Na$ .” U. S. P. The structural formula may be represented as follows:



For description and standards see the U. S. Pharmacopeia under Phenobarbital Sodium and Phenobarbital Sodium Tablets.

**Actions and Uses.**—The same as those of phenobarbital, except that it may be injected in instances where phenobarbital cannot

be administered orally or where the desired effects of the drug are not produced on oral administration.

**Dosage.**—For hypodermic injection, phenobarbital sodium is used in the form of 20 per cent solution, prepared by dissolving the salt in boiled and cooled distilled water; 2 cc. of the solution contains 0.4 Gm. of phenobarbital sodium.

Phenobarbital sodium may be given hypodermically in doses of 0.1 to 0.3 Gm.

*Caution: Aqueous solutions of phenobarbital sodium are not stable but decompose on standing; on boiling, precipitation occurs.*

**ABBOTT LABORATORIES**

**Phenobarbital Sodium (Powder):** Bulk.

**Phenobarbital Sodium (Powder):** 0.13 Gm. ampuls.

**Phenobarbital Sodium (Powder):** 0.324 Gm. in 2 cc. ampuls.

**Tablets Phenobarbital Sodium:** 65 mg. (hypodermic) and 0.1 Gm.

**ENDO PRODUCTS, INC.**

**Sodium Phenobarbital Solution in Propylene Glycol:** 0.16 Gm. in 2 cc. ampuls and 0.325 Gm. in 2 cc. ampuls.

**GANE AND INGRAM, INC.**

**Phenobarbital Sodium (Powder):** 30 cc., 60 cc. and 120 cc. bottles.

**Tablets Phenobarbital Sodium:** 109 mg.

**MALLINCKRODT CHEMICAL WORKS**

**Phenobarbital Sodium (Powder):** Bulk.

**MERCK & Co., INC.**

**Phenobarbital Sodium (Powder):** Bulk.

**WINTHROP-STEARNs, INC.**

**Luminal Sodium (Powder):** Bulk.

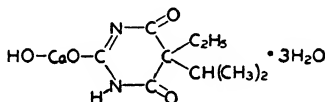
**Solution Luminal Sodium in Propylene Glycol:** 2 cc. ampuls. Each cubic centimeter contains luminal sodium 0.16 Gm., dissolved in propylene glycol. The solution may be administered intramuscularly or subcutaneously, but not intravenously.

**Luminal-Sodium (Powder):** 130 mg. and 324 mg. ampuls.

**Tablets Luminal-Sodium:** 15 mg., 30 mg. and 100 mg. and 60 mg. (hypodermic).

U. S. patent 1,025,872 (May 7, 1912; expired). U. S. trademark 87,327.

**PROBARBITAL CALCIUM.**—**Ipral Calcium-Squibb.**—Calcium 5-ethyl-5-isopropyl barbiturate.—The trihydrated calcium salt of 5-ethyl-5-isopropylmalonyl urea. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—Probarbital calcium has the therapeutic properties of barbituric acid. It is soluble in water and is absorbed promptly. It is claimed that it is excreted rapidly, but some action commonly persists for twenty-four hours.

Probarbital calcium is used as a hypnotic to combat restlessness, irritability and sleeplessness. It is claimed that tolerance to probarbital calcium is not developed readily, but that its action is so persistent that a patient frequently sleeps on the night succeeding that when the hypnotic was administered.

The drug should be administered sparingly to patients in whom the proposed operation may lead to circulatory collapse and shock. For severe trauma or in the presence of shock the drug should not be administered. It is also contraindicated in patients with pulmonary disease and pulmonary edema and in cases of uncontrolled diabetes.

**Dosage.**—From 0.12 to 0.25 Gm. followed by a cupful of hot water, tea or milk. For pre-anesthetic sedation the recommended dose is 0.25 to 0.5 Gm.

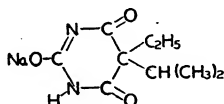
**Caution:** *Aqueous solutions of probarbital salts are not stable but decompose on standing; on boiling, precipitation occurs.*

E. R. SQUIBB & SONS

**Tablets Ipral Calcium:** 50 mg. and 0.13 Gm.

U. S. patents 1,255,951 (Feb. 12, 1918; expired); 1,576,014 (March 9, 1926; expired). U. S. trademark 208,813.

**PROBARBITAL SODIUM.**—**Ipral Sodium-Squibb.**—Sodium 5-ethyl-5-isopropylbarbiturate.—The sodium salt of 5-ethyl-5-isopropylmalonylurea. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions, Uses and Dosage.**—See monograph on Probarbital Calcium.

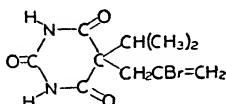
**E. R. SQUIBB & SONS**

**Elixir Ipral Sodium:** 13 Gm. in 1,000 cc.; 5 cc. is equivalent to 65 mg. of Ipral Sodium.

**Tablets Ipral Sodium:** 0.25 Gm.

U. S. patents 1,255,951 (Feb. 12, 1918; expired); and 1,576,014 (March 9, 1926; expired). U. S. trademark 208,813.

**PROPALLYLONAL.** — Nostal-Ames. — 5-Isopropyl-5-β-bromallyl barbituric acid.—5-isopropyl-5-β-bromallyl malonyl-urea. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses of propallylonal are essentially similar to those of barbital, but propallylonal is more active than barbital and is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as an hypnotic.

**Dosage.**—As a sedative: 50 mg. to 0.1 Gm. As an hypnotic: 0.1 to 0.3 Gm.; for children, 50 mg. to 0.1 Gm. according to age. Propallylonal should be administered preferably with a hot drink.

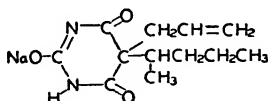
AMES COMPANY, INC.

**Nostal (Powder):** Bulk.

**Tablets Nostal:** 0.1 Gm.

U. S. patent 1,622,129 (March 22, 1927; expired). U. S. trademark 270,750.

**SECONAL SODIUM-Lilly.**—Sodium 5-allyl-5-(1-methyl-butyl) barbiturate. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses of Seconal Sodium are essentially those of barbital but it is described as a short-acting barbiturate. It is more active than barbital and is used in correspondingly smaller doses.

**Dosage.**—The average adult dose is from 0.1 to 0.2 Gm. When oral administration is contraindicated, Seconal Sodium may be administered rectally. Smaller doses of Seconal Sodium

are sedative, larger doses are hypnotic. For use in obstetrics and as a pre-anesthetic sedative the following dosage has been suggested: In obstetrics, an initial dose of 0.3 Gm. followed by 0.1 Gm. to 0.2 Gm. doses at appropriate intervals up to a total of no more than 1.2 Gm. within a 12 hour period; as a pre-anesthetic agent, 0.2 Gm. to 0.3 Gm. one-half to one hour before the patient is sent to the operating room.

#### ELI LILLY AND COMPANY

##### Seconal Sodium (*Powder*): Bulk.

**Elixir Seconal Sodium:** Each 100 cc. contains approximately 0.44 Gm. of seconal in a vehicle containing alcohol, glycerin, water and aromatics; methenamine is present for the purpose of increasing the solubility of the seconal.

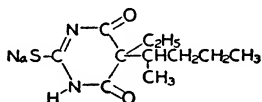
**Pulvules Seconal Sodium:** 50 mg. and 0.1 Gm.

**Suppositories Seconal Sodium:** 0.13 Gm. and 0.2 Gm.

**Seconal Sodium (*Sterile Powder*):** 0.25 Gm. and 0.5 Gm. Dry powder used to prepare a 5 per cent solution by the addition of 5 cc. or 10 cc., respectively, of sterile distilled water.

U. S. patent 1,954,429 (April 10, 1934; expires 1951). U. S. trademark 328,662.

**THIOPENTAL SODIUM-U. S. P.—Pentothal Sodium-Abbott.**—Sodium 5-ethyl-5-(1-methylbutyl) thiobarbiturate. The monosodium salt of 5-ethyl-5-(1-methylbutyl) thiobarbituric acid. The structural formula may be represented as follows:



For descriptions and standards see the U. S. Pharmacopeia under Thiopental Sodium and Thiopental Sodium.

**Actions and Uses.**—The actions and uses of thiopental sodium are essentially similar to those of pentobarbital sodium except that thiopental sodium is effective in smaller doses and the action is of briefer duration. When injected it is a quick-acting, general anesthetic with an early recovery period which is occasionally marked by mental depression lasting for a few hours. It may be emphasized that the intravenous use of barbiturates may be a valuable procedure; but such use is potentially dangerous and should be undertaken only by experts for short operations. The use of thiopental sodium is not recommended in major operative procedures requiring long anesthesia or for office procedures. It should be employed only by competent, experienced anesthetists or surgeons who have at their hands facilities to combat problems involving respiratory depression, laryngospasm, and carbon

dioxide-oxygen balance. Atropine should be administered as premedication.

**Dosage.**—Two or three cc. of a 2½ per cent solution is injected in about ten or fifteen seconds. The injection is then stopped to permit the complete effect to appear, which requires from thirty to thirty-five seconds. If relaxation has not occurred, an additional 2 or 3 cc. may be injected at the same rate as before.

**Caution:** *Aqueous solutions of thiopental sodium are not stable but decompose on standing; on boiling, a precipitation occurs.*

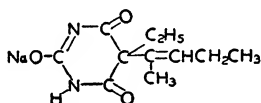
#### ABBOTT LABORATORIES

**Pentothal Sodium:** 0.5 Gm. and 10 Gm. ampuls with 30 mg. and 60 mg. anhydrous sodium carbonate respectively, as buffer; 5.0 Gm. multiple dose ampul with 0.3 Gm., anhydrous sodium carbonate as a buffer.

**Pentothal Sodium (Rectal):** 3 Gm. vials with 0.18 Gm. anhydrous sodium carbonate as a buffer.

U. S. patent 2,153,729 (April 11, 1939; expires 1956). U. S. trademark 334,340.

**VINBARBITAL SODIUM.**—Delvinal Sodium-Sharp & Dohme. — Sodium-5-ethyl-5-(1-methyl-1-butenyl) barbiturate. The structural formula may be represented as follows:



For tests and standards, see Section B.

**Actions and Uses.**—The actions and uses of vinbarbital sodium are similar to those for the intermediate-acting group of barbituric acid derivatives. It has a short induction period and a moderate duration of action. It is used for general sedation and hypnosis, pre-operative sedation, pre-anesthetic hypnosis, obstetrical sedation and amnesia. Its use occasionally gives rise to side effects such as epigastric discomfort, nausea, dizziness, pallor and even fall in blood pressure.

**Dosage.**—As a sedative, 32 mg. repeated three to four times daily; as a sedative and hypnotic, 0.1 Gm. to 0.2 Gm.; as a preoperative hypnotic, 0.1 Gm. to 0.2 Gm.; in psychiatric cases, 0.1 Gm. to 0.4 Gm.; for obstetric sedation and amnesia, 0.2 Gm. to 0.4 Gm., with or without scopolamine. Children must be given correspondingly smaller doses.

**Caution:** *Unbuffered aqueous solutions of vinbarbital sodium are not stable. The powder is hygroscopic, and if capsules are broken or exposed to high humidity the contents are affected by both moisture and carbon dioxide.*

**SHARP & DOHME, INC.**

**Capsules Delvinal Sodium:** 0.1 Gm., 0.2 Gm. and 30 mg.

**Elixir Delvinal Sodium:** 473 cc. bottles. Each 30 cc. contains vinbarbital sodium 0.26 Gm. in a palatable elixir containing alcohol 33 per cent.

**Solution Delvinal Sodium:** 5 cc. ampuls and 20 cc. vials. Each cc. contains vinbarbital sodium 60 mg. in aqueous, 90 per cent propylene glycol solution.



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## CHAPTER XXII

# Serums and Vaccines

Under this heading are described in the following pages agents of a complex biologic nature which are used in diagnosis, in prevention, and in the treatment of disease and which depend for their action on various phases and relations of immunity.

*Federal Regulations.*—The urgent need for control of many of these potent and, in some cases, dangerous products has been partly met by a federal law entitled "An act to regulate the sale of viruses, serums, toxins, and analogous products in the District of Columbia, to regulate interstate traffic in said articles and for other purposes." Under this law the importation, exportation or interstate sale of these products is expressly forbidden unless the manufacturer holds a license issued on the recommendation of the U. S. Public Health Service.

It is to be noted that the protection of the federal law is of avail only in the case of prophylactic and therapeutic preparations which are imported or shipped for exportation or interstate sale. Only products which are licensed under the law referred to and which have not been found to conflict with the rules of the Council will be found listed here. In purchasing the products for use, preference should be given to those which have been kept continually at a low temperature.

*Dating of Biologic Products.*—The federal law requires that each package of biologic products be marked with an expiration date, "the date beyond which the contents cannot be expected beyond reasonable doubt to yield their specific result." The regulations framed under this law, as outlined below, prescribe for each class of product how long after date of manufacture or issue this expiration date may be; but the temperature at which the product is kept after leaving the manufacturer's hands cannot be controlled. Physicians would do well to secure their biologic products from stocks which are shown by actual continuous thermometer records to have been kept in cold storage. This is particularly applicable to the more rapidly deteriorating products, such as smallpox vaccine and the various immune serums.

Official potency standards have been established, or official potency tests are made at the National Institute of Health prior to the release of each lot, for the following products: botulinus antitoxin, diphtheria antitoxin, *Cl. histolyticum* antitoxin, *Cl. oedematiens* antitoxin, staphylococcus antitoxin, tetanus antitoxin, scarlet fever streptococcus antitoxin, *perfringens* antitoxin, vibron, septicæ antitoxin, diphtheria toxin-antitoxin mixture,

diphtheria toxoids, tetanus toxoids, antidyenteric serum, anti-meningococcic serum, type specific antipneumococcic serums, bacterial vaccines prepared from the typhoid bacillus, diphtheria toxin for the Schick test and scarlet fever streptococcus toxin for the Dick test and for immunization. For these products the dating of each lot is based on the last test for potency, that is, the date of manufacture is taken as the last date of satisfactorily passing a potency test. For all other biologic products, the testing for potency is on a less satisfactory basis, and the date of manufacture is counted as the date of removal from the animal in case of animal products, or the date of cessation of growth in the case of other products. For the purpose of determining the expiration date, the date of issue may be used instead of the date of manufacture, provided the product has been kept between the date of manufacture and the date of issue not longer than the following periods, at the corresponding temperature: twenty-four months constantly below 0 C., or twelve months constantly below 5 C., or six months constantly below 10 C., or three months constantly below 15 C.

*Added Preservatives.*—The safeguarding of serums, vaccines, etc., against bacterial contamination usually requires the addition of some antiseptic. The most commonly used antiseptics are cresol (0.4 per cent), phenol (0.5 per cent), glycerin, and organic mercury compounds.

*Untoward Effects.*—The use of serums and serum preparations is sometimes followed by certain untoward manifestations. These are due usually to sensitivity of the individual to animal products especially horse serum and in certain cases may be avoided by the use of serums which have been altered by the action of enzymes or by using serums from the bovine species or from sheep or goats. Serums and antitoxins, unless made by the inoculation of the horse, must show on the label the species of animal used.

Reports have appeared in the recent medical literature of the favorable effect of procaine in the treatment of serum sickness: (*J. A. M. A.* April 13, 1946, 130:990 and *J. A. M. A.* August 17, 1946, 131:1274). This evidence needs further confirmation.

The following outline sets forth the classification of the preparations as described in this chapter:

### SERUMS

#### NORMAL SERUMS OR NORMAL BLOOD DERIVATIVES

- Citrated normal human plasma
- Human immune globulin
- Normal human serum

#### IMMUNE SERUMS

- Antitoxic serums*

- Antitoxins*

- Antivenin (*Crotalus*)

- Antivenin (*Iatroedectus mactans*)

Botulism antitoxin  
Diphtheria antitoxin  
Gas gangrene antitoxin (*Cl. perfringens* and *Cl. septicum*)  
Gas gangrene antitoxin (*Cl. perfringens*, *Cl. septicum*,  
*Cl. novyi*, *Cl. sordellii* and *Cl. histolyticum*)  
Tetanus-gas gangrene antitoxin (*Cl. welchii*, *Cl. septicum*  
and *Cl. tetani*)  
Scarlet fever streptococcus antitoxin  
Staphylococcus antitoxin  
Tetanus antitoxin  
Tetanus antitoxin, Bovine  
*Antibacterial serums*  
  Antianthrax serum  
  Antidysenteric serum  
  Antierysipeloid serum  
  Antimeningococcic serum

#### NATURALLY PRODUCED ANTIBODIES

Human measles immune serum  
Human scarlet fever immune serum  
Pertussis immune serum (human)

#### VACCINES

Active immunization, General considerations.

#### ATTENUATED LIVING VIRUSES, OR KILLED VIRUSES

Influenza virus vaccine Types A and B.  
Rabies vaccine  
Rabies vaccine (Cumming)  
Rabies vaccine (Harris)  
Rabies vaccine (Pasteur)  
Rabies vaccine (Semple)  
Rabies vaccine (Semple), chloroform killed

#### BACTERIAL TOXINS

Scarlet fever streptococcus toxin  
Scarlet fever streptococcus toxin, tannic acid precipitated

#### BACTERIAL TOXINS, MODIFIED

Diphtheria toxin-antitoxin mixture  
Diphtheria toxoid  
Diphtheria toxoid, alum precipitated, refined  
Diphtheria toxoid, tetanus toxoid, alum precipitated, com-  
bined  
Staphylococcus toxoid  
Tetanus toxoid  
Tetanus toxoid, alum precipitated, refined

#### BACTERIAL VACCINES

Brucella vaccine (undulant fever vaccine)  
Cholera vaccine  
Pertussis vaccine  
Pertussis vaccine alum precipitated

- Pertussis vaccine and antitoxin, combined
- Pertussis vaccine combined with diphtheria toxoid
- Pertussis vaccine combined with diphtheria and tetanus toxoids
- Plague vaccine
- Staphylococcus vaccine
- Typhoid vaccine
- Typhoid and paratyphoid vaccine

**TOXOID-VACCINE MIXTURES**

- Staphylococcus toxoid-vaccine mixture

**DIAGNOSTIC AGENTS**

- Diphtheria toxin for Schick test
- Scarlet fever streptococcus toxin for Dick test
- Scarlet fever streptococcus antitoxin for Schultz-Charlton test
- Trichinella extract
- Tuberculins
  - Purified protein derivative of tuberculin
  - Old tuberculin
  - New tuberculin, B. E.
  - New tuberculin, B. E., dried
  - New tuberculin, T. R.
  - New tuberculin, T. R., dried
  - Tuberculin Denys

**SERUMS****Normal Serums or Normal Blood Derivatives**

This section lists those preparations derived from normal blood, such as plasma, serum or globulins. Any antibodies which the preparations may contain have been produced naturally in the body. There is definite evidence that human serum preparations may by carrying a virus, be instrumental in leading to the development of a form of infectious jaundice. They may also lead to reactions of the type usually regarded as allergic.

**BLOOD GROUP SPECIFIC SUBSTANCES A AND B.**—A sterile solution of polysaccharide-amino-acid complexes, capable of reducing the titer of the anti-A and anti-B isoagglutinins of group O donor blood. Blood group specific substance A is isolated as a precipitate from a tryptic digest of hog gastric mucin. Group specific substance B is isolated as a precipitate from a tryptic digest of the glandular portion of horse gastric mucosa.

*Actions and Uses.*—Blood Group Specific Substances A and B, when added to group O blood, renders the latter safe for transfusion into patients having other blood groups. While this eliminates reaction attributable to the corresponding isoagglutinins, it should be kept in mind that group O blood may continue to

give rise to reactions due to pyrogens, Rh incompatibility, and immunologic unknowns.

**Dosage.**—Blood Group Specific Substances A and B may be added to group O blood just prior to administration or at the time of collection and storage. One transfusion unit (10 cc.) is capable of reducing the anti-B and anti-B isoagglutinin titer of 500 cc. of group O blood to at least one-fourth of its original titer.

SHARP & DOHME, INC.

**Blood Group Specific Substances A and B:** 10 cc. vials. Preserved with phenol 0.3 per cent.

U. S. patent reissue No. 22208 (Expiration Date July 14, 1959).

**HUMAN IMMUNE GLOBULIN-U. S. P.**—Measles Prophylactic.—Placental Extract.—“A sterile solution of antibodies obtained from the placental blood and the placentae expelled by healthy women (*Homo sapiens*). Each preparation shall be composed of a pool from at least ten individuals. Human immune globulin complies with the requirements of the National Institute of Health of the United States Public Health Service.”  
**U. S. P.**

For description and standards see the U. S. Pharmacopeia under Globulin Human Immune.

**Actions and Uses.**—Human immune globulin is useful in the prevention and modification of measles. It is equivalent in usefulness to convalescent serum but has the advantage of universal availability. It has the disadvantage of producing reactions not always mild. Most reactions, however, can be avoided by the administration of the proper dosage, which is necessarily modified in accordance with the stage of the incubation period or the prodromal stage of the disease. It is useful in the prevention of measles in institutional cases in larger doses than those given for modification. Prevention is, of course, less desirable than modification except where younger children ill with other diseases are apt to contract measles by exposure to a modified case. Otherwise it is more desirable to permit a child to have mild measles so that immunization occurs rather than to prevent the disease and leave the child nonimmune to subsequent attacks of the disease. Protection should not be attempted until definite exposure has taken place. Attempts to avoid reactions have led to refinement and concentration of the product and even to its oral administration; the latter cannot be advocated on the basis of the evidence which is available at present.

**Dosage.**—The amount of human immune globulin which should be injected in a given case depends on the following factors:

1. Whether modification or prevention is desired.
2. The age and general condition of the patient.
3. The intimacy of exposure.

Careful consideration of the available literature is necessary to evaluate properly these factors and determine an entirely

satisfactory dosage, and even then it is not always possible to be certain of not obtaining prevention when modification is desired and vice versa. The following doses are recommended merely as a general pattern and are subject to adjustment in accordance with the factors listed above: for prevention, 2 to 10 cc.; for modification, 2 to 5 cc.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Immune Serum Globulin (Human):** 2 cc. and 10 cc. vials. Preserved with 0.5 per cent of phenol.

**Immune Serum Globulin (Human):** 2 cc. vials. Preserved with Merthiolate, 1:10,000.

SHARP & DOHME, INC.

**Immune Serum Globulin (Human):** 2 cc. and 10 cc. vials. Preserved with 0.5 per cent of phenol.

WYETH, INCORPORATED

**Immune Serum Globulin (Human):** 2 cc. and 10 cc. vials. Preserved with 0.1 per cent of phenol and 0.01 per cent of Merthiolate.

**CITRATED NORMAL HUMAN PLASMA-U. S. P.—**  
Normal Human Plasma.—“The sterile plasma obtained by pooling approximately equal amounts of the liquid portion of citrated whole blood from eight or more humans (*Homo sapiens*, Linné) who have been certified by a qualified doctor of medicine as free from any disease which is transmissible by blood transfusion at the time of drawing the blood. It must be emphasized that despite all precautions taken, plasma as well as serum and whole blood may carry the virus responsible for homologous serum jaundice. Each bleeding is drawn under aseptic precautions into individual sterile centrifuge bottles already containing 50 cc. of a sterile, 4 per cent solution of sodium citrate in isotonic solution of sodium chloride for each 500 cc. of whole blood. The cell-free plasma is separated by centrifugation, and transferred to a pool by means of a closed system. Sterility tests are made, a preservative is added, and the plasma is distributed into final containers through a closed system. Citrated normal human plasma complies with the requirements of the National Institute of Health of the United States Public Health Service.

“Citrated normal human plasma may be dispensed as liquid plasma, as frozen plasma, or as dried plasma. Citrated normal human plasma must be free from harmful substances detectable by animal inoculation, and must not contain an excessive amount of preservative.” U. S. P.

For description and standards see the U. S. Pharmacopeia under Plasma, Citrated Normal Human.

**Actions and Uses.**—Citrated normal human plasma is administered in the treatment of surgical and traumatic shock, in the

treatment of burns when loss of available plasma occurs, to combat hypoproteinemia, and as a temporary substitute for whole blood in the treatment of hemorrhage when whole blood is not immediately available. Plasma and serum may be considered satisfactory substitutes for whole blood *except in those cases in which the administration of red blood corpuscles is regarded as essential.*

**Dosage.**—Citratd normal human plasma, whole or restored, is administered intravenously in amounts equivalent to those employed in the transfusion of whole blood, but it should be remembered that plasma represents approximately one-half the total volume of whole blood. Average dose is 500 cc. intravenously (U. S. P.).

#### CUTTER LABORATORIES

**Normal Human Plasma:** 300 cc. bottles. 1:10,000 sodium ethylmercuri-thiosalicylate is used as a preservative.

#### SAMUEL DEUTSCH SERUM CENTER, MICHAEL REESE RESEARCH FOUNDATION

**Normal Human Plasma (Citratd):** 60 cc. and 300 cc. bottles. Contains dextrose in final concentration of 5 per cent.

#### HYLAND LABORATORIES

**Normal Human Plasma (Dried):** 50 cc. and 500 cc. bottles. Containing an amount (preserved with phenylmercuric borate 1:25,000) to yield 50 cc., 250 cc. and 500 cc. respectively of restored plasma, packaged with corresponding sized bottles of distilled water as diluent (preserved with citric acid 0.1 per cent) and a double-ended needle.

**Normal Human Plasma (Citratd):** 300 cc. bottle containing dextrose 5 per cent and containing 1:15,000 phenylmercuric borate.

#### SHARP & DOHME, INC.

**Lyovac Normal Human Plasma:** 50 cc. vacule vial containing a sufficient amount (preserved with phenylmercuric borate 1:25,000) to yield 50 cc. of restored plasma, packaged with a 50 cc. bottle of distilled water as a diluent (containing 0.1 per cent citric acid).

**Lyovac Normal Human Plasma:** 250 cc. bottles containing a sufficient amount (preserved with 1:25,000 phenylmercuric borate) to yield 250 cc. of restored plasma; packaged with a 250 cc. bottle of distilled water for dilution (containing 0.1 per cent citric acid) and equipment for intravenous injection.

**Lyovac Normal Human Plasma:** 500 cc. bottle containing a sufficient amount (preserved with phenylmercuric borate 1:25,000) to yield 500 cc. of restored plasma, packaged with a

500 cc. bottle of distilled water as a diluent (containing 0.1 per cent citric acid) and equipment for intravenous injection.

U. S. patents Reissue 20,969 (Jan. 3, 1939; expires 1956); 2,085,391, 2,085,392 (June 29, 1937; expires 1954); 2,099,659 (Nov. 16, 1937; expires 1954); 2,149,304 (March 7, 1939; expires 1956); 2,163,996 (June 27, 1939; expires 1956); 2,176,004 (Oct. 10, 1939; expires 1956); 2,198,752 (April 30, 1940; expires 1957); 2,199,815, 2,199,816, 2,199,817 (May 7, 1940; expires 1957); 2,225,774 (Dec. 24, 1940; expires 1957); 2,340,102 (Jan. 25, 1944; expires 1961). U. S. trademarks 357,071 and 380,366.

**NORMAL HUMAN SERUM-U. S. P.**—"The sterile serum obtained by pooling approximately equal amounts of the liquid portion of coagulated whole blood from eight or more humans (*Homo sapiens*) who have been certified by a qualified doctor of medicine as free from any disease which is transmissible by blood transfusion at the time of drawing the blood. It must be emphasized that despite all precautions taken, serum as well as plasma and whole blood may carry the virus responsible for homologous serum jaundice. Each bleeding is drawn under aseptic precautions into individual sterile centrifuge bottles and allowed to coagulate for at least 12 hours and not more than 24 hours. The cell-free serum is separated by centrifugation, and transferred to a pool by means of a closed system. Sterility tests are made, a preservative is added, the serum is passed through a bacteria-excluding filter and finally distributed into the final containers through a closed system.

*Caution: Each lot of serum shall be aged in the liquid state for at least 28 days at 2 to 10 C. subsequent to the removal of the clot and prior to its use as liquid serum, or prior to freezing and drying.*

Normal Human Serum complies with the requirements of the National Institute of Health of the United States Public Health Service." U. S. P.

For description and standards see the U. S. Pharmacopeia under Serum Normal Human.

*Actions, Uses and Dosage.*—See Citrated normal human plasma.

SAMUEL DEUTSCH SERUM CENTER, MICHAEL REESE RESEARCH FOUNDATION

**Normal Human Serum:** 250 cc. bottle. Phenylmercuric borate 1:15,000 is used as a preservative.

**Normal Human Serum (Diluted):** 250 cc. bottle. Diluted with 250 cc. of isotonic solution of sodium chloride. Phenylmercuric borate 1:15,000 is used as a preservative.

HYLAND LABORATORIES

**Normal Human Serum:** 250 cc. bottle. Preserved with 1:15,000 phenylmercuric borate.



**NORMAL HUMAN SERUM ALBUMIN.**—The albumin fraction of normal adult human plasma. The finished product contains 25 per cent of albumin and not more than 0.33 per cent of sodium. It complies with the minimum requirements of the National Institute of Health for serum albumin and conforms to the specifications of the Commission on Plasma Fractionation.

*Actions and Uses.*—To reduce edema and raise the serum protein level in hypoproteinemia; also used in the treatment of shock.

*Dosage.*—Approximately one cc. per pound body-weight given at a rate not greater than 2 cc. per minute, usually to be accompanied by normal salt solution or 5 per cent glucose.

CUTTER LABORATORIES

**Normal Human Serum Albumin (Salt-Poor) 25% : 20 cc.** bottles, containing 5 Gm. of albumin with not more than 0.33 per cent of sodium in a buffered diluent, osmotically equivalent to 100 cc. of plasma. No preservative added.

Licensed by Research Corporation. U. S. patent No. 2,390,074.

## Immune Serums for Prophylactic or Therapeutic Purposes

### ANTITOXIC SERUMS

Antibodies are usually directed against the toxins or other soluble products of bacteria or against the bacteria themselves. All the antibodies enumerated below are formed in the blood serum of the larger domestic animals by active immunization; that is, by injecting the animal with an antigen. The animal is then bled to furnish the serum, which afterward may be purified, in the case of the antitoxins and some other immune serums, to remove as many inactive substances as possible, leaving the antibody in a concentrated form.

### ANTITOXINS

The antitoxins are among the most useful of the antibodies. As the name implies, they antagonize toxins. Though toxins may be secreted by plants other than the bacteria and by some animals, e.g., the snake, the typical toxins are the soluble poisons produced by diphtheria and tetanus bacilli.

Diphtheria and tetanus are dangerous diseases almost entirely on account of the action of these toxins, and conversely, their prevention or cure, when the organisms have once gained entrance to the body, depends on the work of the particular antitoxin. Though the presence of the toxin stimulates the body to produce antitoxin, this active immunity may not be enough to save life; and, at any rate, assistance by the injection of antitoxin, ready made in the blood serum of another animal, hastens the cure or may prevent the disease.

In some individuals, eruptions occur after injection of antitoxin, rarely swelling and pain in the joints; in others, more

severe symptoms have been observed and in a few instances sudden death has occurred. These conditions are due, not to the antitoxin but to the horse serum in which it is contained.

Some preparations of antitoxin globulin-modified differ from U. S. P. antitoxins in that the refinement process includes a selective digestion of the proteins of the antitoxic horse plasma. As a result of this process up to 80 per cent coagulable protein is digested. The remaining portion of globulin associated with antitoxin becomes highly despecified. Injections of globulin-modified antitoxin are followed by far fewer instances of serum-sickness, than are injections of antitoxin contained in unaltered horse serum globulin.

**ANTIVENIN (CROTALUS).—CROTALUS ANTITOXIN.—NORTH AMERICAN ANTI-SNAKE BITE SERUM.**—An antitoxic serum prepared by immunizing animals against the venom of snakes of the crotalus family.

*Actions and Uses.*—Tests on animals show that the venom of certain snakes may be neutralized by the employment of a serum obtained from animals that have been injected with venom from a snake of the same family. Crotalus antitoxin is used to neutralize the venom injected by the bite inflicted by members of the crotalus family.

*Dosage.*—The serum is administered intramuscularly or subcutaneously; in cases seen late or in the presence of severe symptoms it may be administered intravenously. Certain observations seem to show that there is great advantage in giving the serum in the vicinity of the bite. Use of the antitoxin never should be allowed to replace first aid measures, especially local incisions and suction. Perhaps 50 cc. of serum is as small an amount as is likely to prove beneficial.

**ANTIVENIN (LATRODECTUS MACTANS).** — An antitoxic serum prepared by immunizing horses against the venom of the black widow spider. (*Latrodectus mactans*).

*Actions and Uses.*—This material, which is standardized on the basis of its ability to neutralize the venom of the black widow spider when the two are injected simultaneously in mice, is claimed to be indicated in the treatment of patients suffering from symptoms due to bites inflicted by the black widow spider (*Latrodectus mactans*). Prior to use, tests for serum sensitivity should be made, test material consisting of 1:10 dilution of isotonic solution of normal equine serum, which is injected intradermally. If there is a positive skin reaction, an eye test consisting of placing a few drops of the test material on the conjunctiva and watching for ten minutes should be undertaken. If there is a negative result from the skin test, the therapeutic serum can be administered. However, if there is a positive reaction in the eye following the positive skin test, serum therapy should be avoided. If there is a positive skin test and a negative eye test, the individual may be desensitized before

administering the serum. The amount of material injected into the skin for the intradermal test should be not more than 0.02 cc. of the test material. The result can be evaluated in ten minutes, a positive reaction consisting of an urticarial wheal surrounded by a zone of erythema.

Associated treatment includes hot plunge baths, intravenous injection of magnesium sulfate, 20 cc. of 10 per cent solution, or intravenous injection of 10 per cent calcium gluconate. Barbiturates may be used for restlessness. Apparently nothing is gained by local treatment at the site of the bite.

*Dosage.*—An injection of 2.5 cc. of serum is administered intramuscularly.

SHARP & DOHME, INC.

**Lyovac Antivenin (*Latrodectus mactans*):** 'Vacule' vial containing a sufficient amount of lyophilized antivenin to yield 2.5 cc. of restored double-concentrated antivenin with phenol 0.35 per cent as a preservative; packaged with a 2.5 cc. vial of distilled water and one 1 cc. vial of normal horse serum (diluted 1:10) as test and desensitizing material.

A lyophilized antitoxic serum prepared by injecting horses with venom of black widow spiders (*Latrodectus mactans*).

A process of lyophilization consists in the following: The antivenin in specially designed final containers is immersed in a freezing mixture to congeal the substance rapidly with the least molecular rearrangement. The container is then subjected to a high vacuum to accomplish dehydration, which is continued until the residual moisture content is less than 1 per cent, and finally sealed under vacuum.

**BOTULISM ANTITOXIN.**—An antitoxic serum prepared by immunizing animals against the toxins of two types of *Clostridium botulinum*.

*Actions and Uses.*—For prophylaxis and treatment of botulism. The clinical value of the antitoxin is uncertain.

*Dosage.*—Prophylactic: subcutaneous injections of not less than 2,500 units of bivalent antitoxin. Therapeutic: intravenous injection of not less than 10,000 units of the bivalent antitoxin to be repeated as indicated by the nature of the case.

**DIPHtheria ANTITOXIN-U. S. P.**—"A sterile aqueous solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal which has been immunized against diphtheria toxin. Diphtheria Antitoxin has a potency of not less than 500 antitoxic units per cc. It complies with the requirements of the National Institute of Health of the United States Public Health Service." U. S. P.

For description and regulations see the U. S. Pharmacopeia under Diphtheria Antitoxin.

*Actions and Uses.*—For prophylaxis and treatment of diphtheria.

*Dosage*.—"Parenteral, therapeutic, 20,000 units; prophylactic, 1,000 units." U. S. P.

**BIVALENT GAS GANGRENE ANTITOXIN-U. S. P.**  
—"A sterile solution of antitoxic substances obtained from the blood of healthy animals, which have been immunized against *Clostridium perfringens* and *Clostridium septicum* toxins. Each package of Bivalent Gas Gangrene Antitoxin shall contain not less than 10,000 antitoxic units of each of the component antitoxins. Bivalent Gas Gangrene Antitoxin complies with the requirements of the National Institute of Health of the United States Public Health Service." U. S. P.

For description and regulations see the U. S. Pharmacopeia under Gas Gangrene Antitoxin, Bivalent.

*Actions and Uses*.—Used in prevention and treatment of gas gangrene. The clinical value of this antitoxin is questionable.

*Dosage*.—Therapeutic: 10,000 to 40,000 units each of *Cl. perfringens* and *Cl. septicum* intramuscularly or intravenously, preferably the latter, repeated every twelve to twenty-four hours depending on the symptoms in the individual case.

#### CUTTER LABORATORIES

**Gas Gangrene Antitoxin:** Bottle containing 10,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins. Preserved with 0.35 per cent tricresol.

#### ELI LILLY AND COMPANY

**Gas Gangrene Antitoxin Concentrated (Combined):** Vial containing 10,000 each of *Cl. perfringens* and *Cl. septicum* antitoxins.

**PENTAVALENT GAS GANGRENE ANTITOXIN-U. S. P.**—"A sterile solution of antitoxic substances obtained from the blood of healthy animals which have been immunized against the toxins of *Clostridium perfringens*, *Clostridium septicum*, *Clostridium oedematiens* (Novyi), *Clostridium bifermentans* (Sordelli), and *Clostridium histolyticum*. Each package of Pentavalent Gas Gangrene Antitoxin shall contain not less than 10,000 units each of *Clostridium perfringens* and *Clostridium septicum* antitoxins, 3,000 units of *Clostridium histolyticum* antitoxin, and 1,500 units each of *Clostridium oedematiens* (Novyi) and *Clostridium bifermentans* (Sordelli) antitoxins. Pentavalent Gas Gangrene Antitoxin complies with the requirements of the National Institute of Health of the United States Public Health Service." U. S. P.

For description and regulations see the U. S. Pharmacopeia under Gas Gangrene Antitoxin, Pentavalent.

*Actions and Uses*.—Used in prevention and treatment of gas gangrene. The clinical value of this antitoxin is questionable.

*Dosage*.—The minimum therapeutic dose is 10,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins, and, optionally, 1,500 units each of *Cl. novyi* and *Cl. sordellii* antitoxins and

3,000 units of *Cl. histolyticum* antitoxin intravenously. From one to four times this dose may be given initially and supplemented by additional injections in one to four hours or longer as indicated by the symptoms.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Gas Gangrene Antitoxin Globulin-Modified (Polyvalent):** Vial containing 10,000 units each of *Cl. perfringens* and *Vibrio septique* antitoxins, 1,500 units each of *Cl. novyi* and *sordellii* antitoxins, and 3,000 units of *Cl. histolyticum* antitoxin. Preserved with 0.4 per cent phenol and 1-20,000 phenylmercuric borate.

**TRIVALENT GAS GANGRENE ANTITOXIN.** U. S. P.—“A sterile solution of antitoxic substances obtained from the blood of healthy animals which have been immunized against the toxins of *Clostridium perfringens*, *Clostridium septicum* and *Clostridium oedematiens* (Novyi). Each package of Trivalent Gas Gangrene Antitoxin contains not less than 10,000 units of *Clostridium perfringens* and *Clostridium septicum* antitoxins and 1500 units of *Clostridium oedematiens* (Novyi) antitoxin. Trivalent Gas Gangrene Antitoxin complies with the requirements of the National Institute of Health of the United States Public Health Service.”

For description and regulations see the U. S. Pharmacopeia under Trivalent Gas Gangrene Antitoxin.

**Actions and Uses.**—Used in prevention and treatment of gas gangrene. The clinical value of this antitoxin is questionable.

**Dosage.**—The minimum therapeutic dose is 10,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins, and optionally, 1,500 units of *Cl. novyi* antitoxin intravenously. From one to four times this dose may be given initially and supplemented by additional injections in one to four hours or longer as indicated by the symptoms.

NATIONAL DRUG COMPANY

**Gas Gangrene Antitoxin Refined and Concentrated Globulin (Trivalent):** Vial containing 10,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins, and 1,500 units of *Cl. oedematiens* (Novyi) antitoxin. Preserved with 0.4 per cent tricresol.

PARKE, DAVIS & COMPANY

**Gas Gangrene Antitoxin Refined and Concentrated (Combined, Trivalent):** Vial containing 10,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins, and 1,500 units of *Cl. novyi* antitoxin. Preserved with 0.5 per cent phenol.

E. R. SQUIBB & SONS

**Gas Gangrene Antitoxin:** Vial containing 10,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins, and 1,500 units

of *Cl. novyi* antitoxin. Preserved with 1:20,000 Merthiolate and 0.25 per cent of phenol.

WYETH, INCORPORATED

**Gas Gangrene Antitoxin, Concentrated and Refined (Trivalent):** Syringe and vial each containing 10,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins, and 1,500 units of *Cl. novyi* antitoxin. Preserved with 0.25 per cent phenol and 0.005 per cent Merthiolate.

**TETANUS AND GAS GANGRENE ANTITOXINS.—U. S. P.**—"A sterile solution of antitoxic substances obtained from the blood of healthy animals which have been immunized against the toxins of *Clostridium tetani* and *Clostridium perfringens* and *Clostridium septicum*. Each package of the Antitoxins shall contain not less than 1,500 units of tetanus antitoxin and not less than 2,000 units of each of the other component antitoxins. Tetanus and Gas Gangrene Antitoxins complies with the requirements of the National Institute of Health of the United States Public Health Service.

For description and regulations see the U. S. Pharmacopeia under Tetanus and Gas Gangrene Antitoxins.

**Actions and Uses.**—Used in prevention of gas gangrene. The clinical value of this antitoxin is questionable except as relates to the tetanus antitoxin present.

**Dosage.**—Prophylactic: 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins by parenteral injection. This dose may be repeated at intervals of from five to seven days depending on the severity of the wound. Local infiltration of the wound may be advisable.

CUTTER LABORATORIES

**Tetanus-Gas Gangrene Antitoxin:** Syringe and vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins. Preserved with 0.35 per cent tricresol.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Tetanus-Gas Gangrene Antitoxin (Globulin Modified):** Vials containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins. Preserved with 0.4 per cent phenol and 1:20,000 phenylmercuric borate.

ELI LILLY AND COMPANY

**Tetanus-Gas Gangrene Antitoxin (Combined):** Vial containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins.

NATIONAL DRUG COMPANY

**Tetanus-Gas Gangrene Antitoxin (Monovalent), Refined and Concentrated Globulin:** Vial containing 1,500 units

of tetanus antitoxin and 4,000 units of *Cl. perfringens* antitoxins. Preserved with 0.4 per cent tricesol.

**Tetanus-Gas Gangrene Antitoxin (Trivalent), Refined and Concentrated Globulin:** Syringe and vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins and 300 units of *Cl. oedematiens* (Novyi) antitoxin. Preserved with 0.4 per cent tricesol.

PARKE, DAVIS & COMPANY

**Tetanus-Gas Gangrene Antitoxin (Combined) Prophylactic Refined and Concentrated (Combined):** Vials containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins. Preserved with 0.5 per cent phenol.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Tetanus-Gas Gangrene Antitoxin (Combined) Pepsin Digestion Refined:** Syringe or vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Clostridium perfringens* and *Clostridium septicum* antitoxins.

E. R. SQUIBB & SONS

**Tetanus-Gas Gangrene Antitoxin:** Vial containing 1,500 units of tetanus antitoxin and 2,000 units each of *Perfringens* and *Vibrio septicum* antitoxins. Preserved with 1:20,000 merthiolate and 0.25 per cent of phenol.

U. S. STANDARD PRODUCTS Co.

**Tetanus-Gas Gangrene Antitoxin, Refined and Concentrated:** Syringe containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins. Preserved with 0.4 per cent of cresol.

WYETH, INCORPORATED

**Tetanus Gas Gangrene Antitoxin (Prophylactic) Refined and Concentrated:** Syringe and vial each containing 1,500 units of tetanus antitoxin and 2,000 units each of *Cl. perfringens* and *Cl. septicum* antitoxins and packaged with a 1 cc. vial of dilute (1:10) antitoxin for determination of sensitivity to horse protein. Preserved with 0.25 per cent phenol and 0.005 per cent Merthiolate.

**SCARLET FEVER STREPTOCOCCUS ANTITOXIN-U. S. P.**—Scarlet Fever Antitoxin.—“A sterile solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal which has been immunized against the toxin produced by the streptococcus regarded as causative of scarlet fever. Scarlet Fever Streptococcus Antitoxin has a potency of not less than 400 antitoxic units per cc. It complies with the requirements of the National Institute of Health of the United States Public Health Service.” U. S. P.

For description and standards see the U. S. Pharmacopeia under Scarlet Fever Streptococcus Antitoxin.

*Actions and Uses.*—There is satisfactory evidence that scarlet fever is caused by hemolytic streptococci and that the administration of a serum containing the antitoxin produced by these organisms favorably influences the course of scarlet fever. It is also believed that temporary immunity against scarlet fever may be established through the use of such a serum, but the prophylactic use generally is not considered advisable. The serum is also used to distinguish the rash of scarlet fever from other rashes by the production of a blanched area at the site of its intradermal injection.

*Dosage.*—Prophylactic: 3,000 U. S. P. H. S. units; therapeutic: 9,000 U. S. P. H. S. units.

PARKE, DAVIS & COMPANY

**Scarlet Fever Streptococcus Antitoxin:** Vials containing 3,000 and 9,000 units, respectively.

**STAPHYLOCOCCUS ANTITOXIN.**—Antitoxin prepared by immunizing horses with staphylococcus toxoid and/or staphylococcus toxin. The antitoxin is standardized on the basis of the international unit which was adopted by the Permanent Commission on Biological Standardization of the Health Organization of the League of Nations in 1934, the unit being the equivalent to approximately 125 original antidermonecrotic units, an antidermonecrotic unit being that amount of antitoxin required to neutralize one necrotizing dose of staphylococcus toxin.

*Actions and Uses.*—Staphylococcus antitoxin is suggested in the treatment of acute and severe staphylococcal infections with or without septicemia. Its use in treatment calls for adequate dosage administered early: most of the antitoxin estimated to be necessary for the entire treatment of the infection should be injected during the first few hours after decision is made to use the serum. Supplementing the use of antitoxin in the more severe types of staphylococcal infections, surgical drainage of accessible foci and transfusions with normal or immune donors should be a part of the treatment. Probably chemotherapeutic preparations should take precedence over this antitoxin in routine treatment.

*Dosage.*—For the treatment of localized infections, 10,000 units. For the treatment of more severe infections, from 30,000 to 100,000 units early during the first day in divided doses, followed by from 20,000 to 100,000 units daily until the pulse rate and temperature have subsided and the blood cultures are sterile for three consecutive days.

**TETANUS ANTITOXIN-U. S. P.**—Purified Antitetanic Serum.—Concentrated Tetanus Antitoxin.—Refined Tetanus Antitoxin.—Antitetanic Globulins.—“Tetanus Antitoxin is a sterile aqueous solution of antitoxic substances obtained from



the blood serum or plasma of a healthy animal which has been immunized against tetanus toxin. Tetanus antitoxin has a potency of not less than 400 antitoxic units per cc. It complies with the requirements of the National Institute of Health of the United States Public Health Service." *U. S. P.*

For description and standards see the U. S. Pharmacopeia under Tetanus Antitoxin.

*Actions and Uses.*—Tetanus antitoxin is highly effective in the prevention of tetanus, but its effectiveness when used in the treatment of the disease is much less certain.

*Dosage.*—By parenteral injection: therapeutic, 20,000 units; prophylactic, 1,500-3,000 units or more; both to be repeated at short intervals as indicated. Intrathecal administration generally is regarded as inadvisable.

#### ANTIBACTERIAL SERUMS

More complex in action than the antitoxins and in general less satisfactory for therapeutic purposes are those antibodies which resist the bacteria themselves. They are believed to act primarily by combining chemically with antigens on the bacterial surfaces, thereby rendering the bacteria susceptible to phagocytosis by polymorphonuclear and mononuclear leukocytes. The sphere of usefulness of the antibacterial sera is open to much discussion, and is in need of constant reevaluation in particular with the progress of chemotherapy.

**ANTI-ERYSIPELOID SERUM.**—A serum containing the antibodies and antibacterial properties for *Erysipelothrix rhusiopathiae* (suis). The serum is prepared from horses subjected to increasing subcutaneous injections of live cultures of the organism. Potency is tested on pigeons in which 0.1 cc. of the serum protects against infection lethal to controls in from three to four days.

*Actions and Uses.*—For treatment of the clinical condition known as erysipeloid, which is not to be confused with erysipelas.

*Dosage.*—It is suggested that from 10 to 20 cc. be administered subcutaneously or intramuscularly and quantities of 0.25 to 0.5 cc. at numerous places about the border of the lesion.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Anti-Erysipeloid Serum (Refined):** 10 cc. vial. Preserved with Merthiolate 1:10,000.

#### Naturally Produced Antibodies

In certain infectious diseases the etiological agent may be of such a nature as to make it impractical to produce a satisfactory immune serum in animals. In the absence of artificially

produced antibodies, the best source of antibodies is from human beings who are convalescing from the specific infectious disease. During convalescence from an active infection an individual's serum usually contains antibodies against the specific infectious agent far in excess of the amount normally present. The amount of antibodies, however, is not as great as when animals are artificially immunized by the repeated injection of antigens. An outstanding attribute of naturally produced antibodies, or convalescent serums, is that their source is from a member of the same species, and thus there is less danger of a reaction to the protein of another species, but reaction may occur even with human serums. Even human serum, however, should be used only where there is definite need, since infectious jaundice has been transmitted through the serum.

**HUMAN MEASLES IMMUNE SERUM-N. F.**—Measles Convalescent Serum.—“Human Measles Immune Serum is sterile serum obtained from the bloods of healthy humans (*Homo sapiens*) who have survived an attack of measles. It complies with the requirements of the National Institute of Health of the United States Public Health Service.” *N. F.*

For description and standards see The National Formulary under Human Measles Immune Serum.

**Actions and Uses.**—Human measles immune serum is administered during the incubation period to prevent or modify the expected attack of measles.

**Dosage.**—To prevent the disease in infants and children of 6 years or under, 10 cc. is given intramuscularly within five days after exposure. For children between 7 and 12 years of age, 15 cc. is given, and for older children and adults 20 cc. is given in like manner.

Whether the serum is given for prevention or modification depends on the number of days the patient has been exposed. If prevention is desired, however, the dosage may have to be increased corresponding to the increase in days after exposure of the patient. If injection is made on the sixth or seventh day after exposure, a high percentage of patients have a modified type of measles which is followed by lasting immunity. It is probable that serum given after the seventh day following the initial exposure has little effect in either preventing or modifying the disease.

The serum may be given either intravenously or intramuscularly. Vacuum dried serum should be given only intramuscularly.

MILWAUKEE SERUM CENTER

**Measles Immune Serum (Human):** 5 cc. and 7.5 cc. vials. Preserved with Merthiolate 1:10,000.

SAMUEL DEUTSCH SERUM CENTER, MICHAEL REESE RESEARCH FOUNDATION

**Human Convalescent Measles Serum:** 5 cc., 7.5 cc. and 20 cc. vials. Preserved with phenylmercuric borate 1:15,000.

**HUMAN SCARLET FEVER IMMUNE SERUM.** N. F.—Scarlet Fever Convalescent Serum.—“Human Scarlet Fever Immune Serum is a sterile serum obtained from the blood of healthy individuals (*Homo sapiens*) who survived an attack of scarlet fever. It complies with the requirements of the National Institute of Health of the United States Public Health Service.” N. F.

For description and regulations see The National Formulary under Serum Human Scarlet Fever Immune.

*Actions and Uses.*—Human scarlet fever immune serum is of value in transferring passive immunity to a patient exposed to scarlet fever. The evidence as to therapeutic activity is conflicting. It may be used in patients sensitive to horse serum, though the antitoxic content of convalescent serum is low. It does not seem wholly adequate to meet septic complications.

*Dosage.*—For prophylaxis in infants and young children under 6 years of age, 10 cc. is given; for children between 6 and 12 years of age, 15 cc., and over 12 years of age and for adults 15 to 20 cc. is given, intramuscularly. If the individual is continuously exposed, it is recommended that a second dose be given ten days after the first injection.

MILWAUKEE SERUM CENTER

**Scarlet Fever Immune Serum (Human):** 10 cc. and 20 cc. vials. Preserved with Merthiolate 1:10,000.

SAMUEL DEUTSCH SERUM CENTER, MICHAEL REESE RESEARCH FOUNDATION

**Human Convalescent Scarlet Fever Serum:** 10 cc. and 20 cc. vials. Preserved with phenylmercuric borate 1:15,000.

**HUMAN SERUM IMMUNE GLOBULIN.** — The gamma globulin fraction of normal adult human plasma. The finished product contains 16.5 per cent of gamma globulin and complies with the minimum requirements of the National Institute of Health and as prepared by an acceptable method.

*Actions and Uses.*—For modification or complete protection against measles.

*Dosage.*—The volume of the dose per pound or body weight is 0.02-0.025 cc. for modification and at least 0.1 cc. for prevention when the product contains 150 mg. of gamma globulin per cc.

## CUTTER LABORATORIES

**Immune Serum Globulin (Human):** 2 cc. vials. Preserved with "merthiolate" 1:10,000.

Licensed by Research Corporation. U. S. patent 2,390,074.

**PERTUSSIS IMMUNE SERUM (HUMAN).**—Hyper-immune Whooping Cough Serum (Human).—A sterile serum prepared from the pooled blood of healthy adult human beings who have had "whooping cough" in childhood and who have received repeated courses of Phase I Pertussis Vaccine. The bloods to be pooled and processed are drawn about one month after a course or courses of vaccine, when the donor's serum agglutination titer is 1:2,560 or higher. The serum may be distributed in the liquid form or as a vacuum dried powder. It complies with the requirements of the National Institute of Health of the United States Public Health Service.

*Actions and Uses.*—Vacuum dried serum may be administered intravenously or intramuscularly for treatment of severe "whooping cough," particularly in infants.

*Dosage.*—For treatment, three 20 cc. doses at 48 hour intervals 20 cc. may be administered. Otherwise two 20 cc. doses may be given at three to five day intervals.

For treatment, three 20 cc. doses at forty-eight hour intervals may be injected. A fourth dose may be necessary. Critically ill infants may be given 60 to 100 cc. intravenously, repeated one or more times.

## HYLAND LABORATORIES

**Pertussis Immune Serum (Human):** Vacuum-dried powder, representing 20 cc. vials. Preserved with sodium ethyl mercuric salicylic 1:35,000. Each vial is packaged with a 10 cc. vial of sterile distilled water.

## PHILADELPHIA SERUM EXCHANGE, CHILDREN'S HOSPITAL OF PHILADELPHIA

**Pertussis Immune Serum (Human):** Vials containing vacuum dried powder representing 20 cc. of Pertussis Immune Serum (Human) preserved with merthiolate 1:35,000. Each vial is packaged with a 10 cc. ampul of sterile distilled water.

## VACCINES

The use of substances for the production of active immunity has the following advantages over passive immunization (use of serums): (a) the antibodies are formed in the patient's own tissues and are not eliminated from the patient's system as rapidly as are antibodies which are contained in serum from another species; for example, the protection conferred by vaccination against smallpox lasts for years, while the prophylactic action of diphtheria antitoxin lasts only two or three weeks; (b) not only are the immune mechanisms of the blood made available, but the fixed cells of the body may also take part

in the immunization process; (c) an individual, who has been actively immunized by the administration of a vaccine, reacts more quickly and to a greater extent than a normal individual, or an individual previously passively immunized, on a subsequent encounter with the antigen. The second response may be against a subsequent dose of the vaccine or an exposure to the antigenic substance in nature.

On the other hand, active immunization is not without its limitations. Considerable time, a matter of several days and even weeks, is required for active immunity to develop in an individual in response to the administration of a vaccine. Often it is necessary for the persons to have immediate protection against a disease, as in the case of a known exposure to the disease. Not all individuals respond to a vaccine, some acquiring a more effective resistance than others. A patient's body may already be overloaded with antigens, as the result of the disease and the introduction of additional antigens, sufficient for an immune response in a normal individual, might in itself prove harmful to the patient.

Antigens may be of various sorts. The vaccine may be the living virus but in an attenuated form, as for example, smallpox vaccine, which is the living virus of smallpox attenuated by passage through the bovine species. The antigenic substances, more commonly, are dead bacterial cells, as for example the extensively used typhoid vaccine. Not infrequently the antigenic substances are products of the bacterial cells, such as the bacterial toxins. In recent times it has been found possible to destroy the toxic effect of bacterial toxins without destroying their ability to stimulate antibody production when introduced into the animal body. Examples of this are toxin-antitoxin mixture and the various toxoids.

### Attenuated Living Viruses or Killed Viruses

#### INFLUENZA VIRUS VACCINE, TYPES A AND B.

—A sterile formaldehyde-killed suspension in isotonic sodium chloride solution of influenza virus consisting of 50 per cent type A virus (equal parts of PR<sup>8</sup> and Weiss strains) and 50 per cent Type B virus (Lee strain) obtained by separate propagation in the extra-embryonic fluids of the developing chick and refined and concentrated either by the red cell elution method or by the centrifugation method. The chosen strains are antigenically distinct and are representative of two known etiologic types of influenza virus, cross immunization with which does not occur. The vaccine is standardized for immunizing potency, purity and sterility in accordance with recommendations of the National Institute of Health.

*Actions and Uses.*—Influenza virus vaccine is used for the production of active immunity against influenza, especially when an epidemic is threatened. Its prophylactic value has been observed only for mild types of influenza and is not fully estab-

lished against severe outbreaks of the disease. Immunity is conferred whose duration ranges from about three months to one year, so that it is advisable to repeat immunization at least every six months when there is need for continued protection. Evidence thus far available indicates that the vaccine is principally effective in reducing the incidence of type B infections; its ultimate protective value in type A influenza is under observation. Its use is recommended against only those strains from which it is prepared and does not render protection against influenza due to other strains of the virus.

In persons allergic to chick or egg protein or who have been sensitized by previous administration of vaccines prepared from chick embryos the use of the vaccine may be potentially dangerous. A careful history to rule out allergy to egg protein should be taken, and, if necessary, an intracutaneous test dose should be given to determine the presence or absence of sensitivity. Patients definitely allergic to chick or egg protein should not be immunized.

*Dosage.*—A single immunizing dose of 1 cc. administered subcutaneously is usually sufficient to induce active immunity within one to two weeks. For children under 12 years of age the dose should not exceed 0.5 cc., with proportionately less for the very young because of greater toxicity of the vaccine in children. A second injection may be indicated if outbreaks of influenza appear in severe form.

ELI LILLY & Co.

**Influenza Virus Vaccine, Types A & B:** Packages of 1 cc. and 5 cc. vials. Preserved with Merthiolate 1:10,000.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Influenza Virus Vaccine, Types A and B, Refined and Concentrated:** Packages of one vial, 5 cc. (five doses). Preserved with sodium ethyl mercuri thiosalicylate 1:10,000.

SHARP & DOHME, INC.

**Influenza Virus Vaccine, Types A and B, Protamine Concentrated and Refined:** Packages of twenty-five, 1 cc. vials. Preserved with sodium ethyl mercuri thiosalicylate 1:10,000.

E. R. SQUIBB & SONS

**Influenza Virus Vaccine, Types A and B, Refined and Concentrated:** Packages of 1 cc. and 10 cc. vials. Preserved with sodium ethyl mercuri thiosalicylate 1:10,000.

**RABIES VACCINE-U. S. P.**—"An uncontaminated suspension of the attenuated, diluted, dried or dead, fixed virus of rabies. The virus is obtained from the tissue of the central nervous system of an animal suffering from fixed virus rabies

infection. Rabies Vaccine complies with the requirements of the National Institute of Health of the United States Public Health Service." U. S. P.

For description and standards see the U. S. Pharmacopeia under Rabies Vaccine.

*Actions and Uses.*—By treatment with rabies vaccine after the bite of a rabid animal, immunity is often established before the incubation period of the disease is completed, and rabies is thus prevented. The treatment fails not infrequently, and in a small percentage of cases it is followed by paralysis, which is usually transient but rarely may be permanent or even fatal.

**RABIES VACCINE (HARRIS).**—Brains and spinal cords of rabbits killed after complete paralysis, following infection with fixed virus, are ground to a paste, frozen with carbon dioxide snow, and rapidly dried *in vacuo*. The resulting dry powder is standardized by the method devised by Dr. Harris and stored *in vacuo* in the cold. One dose is given daily over a period of 10 days or more, doses increasing in unitage up to a maximum.

DR. D. L. HARRIS LABORATORY

**Rabies Vaccine (Harris):** Vacuum sealed tubes packaged in series of ten consecutive doses of increasing potency, with ten vials of physiological solution of sodium chloride to prepare the vaccine suspension, and a Luer syringe with needle.

ELI LILLY AND COMPANY

**Rabies Vaccine (Harris):** 0.5 cc. vials, packaged in series of fourteen doses, with a special syringe unit.

**RABIES VACCINE (PASTEUR) — (PASTEUR ANTIRABIC VACCINE).**—The virus is prepared in accordance with the general method of the U. S. Public Health Service. One-fifth of an inch of dried cord, emulsified in 0.6 cc. of 60 per cent glycerin containing 0.3 per cent tricresol is supplied.

*Actions and Uses.*—Rabies vaccine (Pasteur) is employed for the prophylaxis of rabies.

*Dosage.*—Prophylactic treatment consists of twenty-one doses which are administered at twenty-four hour intervals, and these are sent in three installments of seven doses each. The installments are sent by special delivery mail. The first dose consists of two sections of a cord dried for six days; the second dose consists of two sections of a cord dried for five days; and the third dose two sections of a cord dried for four days. The remaining eighteen doses are prepared from single sections of cords dried as follows: 3, 3, 2, 2, 1, 5, 4, 4, 3, 3, 2, 2, 4, 3, 2, 3, 2, 1 days. They are administered in the order listed. Each dose of the dried cord is diluted with 2.5 cc. of sterile sodium chloride solution in the syringe at the time of injection.

**RABIES VACCINE (CUMMING).**—The vaccine is prepared after preliminary treatment with formalin by dialyzing a 1 per cent suspension of brain tissues from a rabbit dying of rabies (induced by an infection of fixed virus) against running water until the active, virulent virus is destroyed.

*Actions, Uses and Dosage.*—When employed for the prophylaxis of rabies, the treatment is divided into two classes: mild, requiring 14 doses; severe, requiring 21 doses. One dose, 2 cc., is given daily over a period of either 14 or 21 days.

**RABIES VACCINE (SEMPLÉ).**—An antirabic vaccine prepared according to the general method of David Semplé (phenol killed). The brains or brains and spinal cords of rabbits killed on about the sixth day after inoculation with the fixed virus of rabies are triturated with isotonic solution of sodium chloride containing 1 per cent phenol. Various concentrations of nerve tissue are employed. The mixture is strained, incubated at 37 C. for (usually) 24 hours, and then diluted with an equal volume of isotonic solution of sodium chloride, so that the finished product contains a definite amount of brain substance and about 0.5 per cent phenol. Put up in containers, each containing, usually, sufficient material for a daily dose.

*Actions and Uses.*—Rabies vaccine (Semplé) is used in the prophylactic treatment of rabies.

*Dosage.*—0.5 cc., 1 cc., 2 cc. or 3 cc. of the suspended vaccine (depending on the dilution employed) daily over a period of from seven to twenty-eight days depending on the site and severity of the injury. The potency of each dose is approximately the same irrespective of the volume of the suspension in which it is supplied.

#### CUTTER LABORATORIES

**Rabies Vaccine (Semple Method):** 1 cc. vials packaged in units of seven vials. Preserved with 0.5 per cent of phenol.

#### LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Rabies Vaccine (Semple Method):** 2 cc. vials packaged in units of seven and fourteen vials. Preserved with 0.25 per cent of phenol and 1:20,000 Merthiolate.

#### MEDICAL ARTS LABORATORY

**Rabies Vaccine (Phenol Killed):** 2 cc. vials packaged in units of seven and fourteen vials. Preserved with 0.5 per cent of phenol.

#### NATIONAL DRUG COMPANY

**Rabies Vaccine Human (Phenol Killed):** 0.5 cc. vials in packages of seven, without syringe, and packages of fourteen with syringe. Preserved with 0.5 per cent of phenol.



**SHARP & DOHME, INC.**

**Rabies Vaccine (Phenol Killed):** 0.5 cc. vials containing a 20 per cent brain tissue suspension packaged in units of seven vials without syringe, and in units of fourteen vials with or without syringe.

**E. R. SQUIBB & SONS**

**Rabies Vaccine (Semple Method):** 2 cc. vials packaged in units of fourteen vials with syringe and needles. Also packaged in units of seven vials, each containing 2 cc. Preserved with 0.5 per cent of phenol.

**U. S. STANDARD PRODUCTS CO.**

**Rabies Vaccine (Semple Method):** 0.5 cc. vials packaged in units of seven and fourteen vials; 1 cc. vials packaged in units of fourteen vials; 2 cc. vials and 2 cc. syringes each packaged in units of seven and fourteen vials or syringes, and the latter in units of twenty-one syringes. Preserved with 0.5 per cent of phenol.

**WYETH, INCORPORATED**

**Rabies Vaccine (Semple Method):** 2 cc. vials and 2 cc. syringes each packaged in units of fourteen vials or syringes, respectively. Preserved with 0.5 per cent of phenol.

**Rabies Vaccine (Modified Semple Method):** 0.5 cc. vials packaged in units of seven and fourteen vials. Preserved with 0.5 per cent of phenol.

**RABIES VACCINE, CHLOROFORM KILLED.**—Antirabic vaccine prepared according to a modification of the method of David Semple in which the virus is killed with chloroform instead of phenol. The brains and spinal cords of rabbits killed on the sixth or seventh day after inoculation with fixed rabies virus are ground with solution of sodium chloride containing 2 per cent chloroform, to yield a 25 per cent suspension of brain and cord substance. The suspension is kept in the refrigerator at 2 to 5 C. for two months. It is then tested for absence of living virus by rabbit injection. The finished product represents a 25 per cent emulsion.

*Actions, Uses and Dosage.*—Same as Rabies Vaccine (Semple).

**WYETH, INCORPORATED**

**Rabies Vaccine (Chloroform Killed Virus):** 0.5 cc. vials packaged in units of seven and fourteen vials.

**RABIES VACCINE (ULTRAVIOLET IRRADIATION KILLED).**—Brains of rabbits paralyzed by infection with fixed rabies virus are harvested, emulsified and brought to a 10 per cent by weight suspension of tissue in isotonic solution of sodium chloride and filtered through sterile bolting silk. Following filtration, the tissue suspension in a continuously flowing thin

film is exposed to the germicidal rays of an ultraviolet lamp. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

*Actions and Uses.*—Rabies Vaccine (Ultraviolet Irradiation Killed) is employed for the prophylaxis of rabies.

*Dosage.*—1 cc. subcutaneously, daily for 14 to 21 days. For severe exposure bites on face or adjacent to central nervous system, 21 doses, two daily for the first three to seven days and then one dose daily.

PITMAN-MOORE COMPANY

**Rabies Vaccine (Ultraviolet Irradiation Killed):** 1 cc. vials packaged in units of seven vials. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

## Bacterial Toxins

Bacterial toxins are sterile solutions obtained by filtering fluid cultures of the microorganisms through bacteria-excluding filters. The filtrate of toxin contains, in addition to the true bacterial toxin produced during the growth of the microorganisms, metabolic products liberated by the microorganisms during their growth in the medium, soluble components of the bacterial cells, and the unused portions of the culture medium.

**SCARLET FEVER STREPTOCOCCUS TOXIN—U. S. P.**—Dick Test Toxin.—“A sterile solution in a medium containing not more than 1 per cent of peptone but no meat extractive, of certain products including a soluble toxin, resulting from the growth in the broth of suitable strains of hemolytic streptococci. Scarlet Fever Streptococcus Toxin complies with the requirements of the National Institute of Health of the United States Public Health Service.” *U. S. P.*

For description and standards see the *U. S. Pharmacopeia* under Scarlet Fever Streptococcus Toxin.

For diagnostic scarlet fever preparations see under Diagnostic Agents.

*Actions, Uses and Dosage.*—The toxin is used for active immunization. For this purpose it is injected subcutaneously at weekly intervals. The amount of toxin necessary for immunity production varies with the individual. Five to six doses are given, beginning with 162 to 650 skin test doses for the first injection and increasing the amount of toxin in each subsequent injection to a final dose of 100,000 to 120,000 skin test doses. Immunity to the toxin appears in a few weeks and is determined by the absence of a reaction to the intracutaneous test.

NATIONAL DRUG COMPANY

**Scarlet Fever Streptococcus Toxin for Immunization:** 1 cc. vials packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter; 10 cc. vials packaged in units of

five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter. Preserved with 0.5 per cent phenol.

PARKE, DAVIS & COMPANY

**Scarlet Fever Streptococcus Toxin for Immunization:** 1 cc. and 10 cc. vials (one and ten immunizations, respectively), each packaged in units of five vials containing respectively 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cc. The 1 cc. vial, containing 100,000-120,000 skin test doses per cc., also packaged separately.

SHARP & DOHME, INC.

**Scarlet Fever Streptococcus Toxin for Immunization:** 1 cc. and 10 cc. vials (single and ten immunization doses respectively), each packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter; the 1 cc. vial containing 100,000-120,000 skin test doses is also packaged separately.

E. R. SQUIBB & SONS

**Scarlet Fever Streptococcus Toxin for Immunization:** 1 cc. vials packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter; 10 cc. vials packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter and in single vial packages containing 100,000-120,000 skin test doses. Preserved with 0.5 per cent of phenol and buffered with  $\text{KH}_2\text{PO}_4$  and  $\text{NaOH}$ .

U. S. STANDARD PRODUCTS CO.

**Scarlet Fever Streptococcus Toxin for Immunization:** 1 cc. vials packaged in units of five vials containing, respectively, 650, 2,500, 10,000, 30,000 and 100,000-120,000 skin test doses per cubic centimeter; 10 cc. vials packaged in units of six vials containing, respectively, 650, 2,500, 10,000, 30,000, 100,000-120,000 and 100,000-120,000 skin test doses per cubic centimeter. Preserved with phenol 0.5 per cent.

**SCARLET FEVER STREPTOCOCCUS TOXIN, TANNIC ACID PRECIPITATED.**—A sterile buffered solution containing in suspension a tannic acid precipitate of scarlet fever toxin. The finished product is preserved with 0.4 per cent phenol and complies with the requirements of the National Institute of Health of the United States Public Health Service.

**Actions and Uses.**—This tannic acid precipitated toxin is claimed to permit slower absorption and a prolonged antigenic stimulus which permits a reduction in the amount of toxin and size of dose as compared with former methods of immunization.

*Dosage.*—Children receive three intracutaneous injections of 0.1 cc. (dose 1, 750 STD/0.1 cc.; dose 2, 3,000 STD/0.1 cc.; dose 3, 10,000 STD/0.1 cc.) at two week intervals. Some may need a supplemental dose after a four week interval.

Adults may receive 500, 2,000, 6,000 and 10,000 STD at two week intervals. Each vial should be well shaken before use. The toxin should not be used beyond expiration date on label or if it does not resuspend completely on shaking.

WYETH, INCORPORATED

**Scarlet Fever Streptococcus Toxin for Immunization, Tannic Acid Precipitated:** 0.5 cc. single immunization vials and 2 cc. 10 immunization vials packaged in units of three vials (children) contains respectively in each 0.1 cc. 750, 3,000 and 10,000 skin test doses; and in units of four vials (adult) containing in each 0.1 cc. 500, 2,000, 6,000 and 10,000 skin test doses. Also 0.5 cc. single and 2 cc. ten dose vials containing a supplementary dose for children and adults, representing in each 0.1 cc. 10,000 skin test doses. Preserved with phenol 0.4 per cent.

### Bacterial Toxins, Modified

Certain bacterial toxins may be modified so as to retain their capacity for bringing about an immune response while at the same time they are made relatively harmless, or at least their toxicity is greatly decreased. Examples of such modified bacterial toxins are Diphtheria Toxin-Antitoxin Mixture and Diphtheria Toxoid.

#### *Toxin-Antitoxin Mixture*

#### **DIPHTHERIA TOXIN-ANTITOXIN MIXTURE.—**

A mixture of diphtheria toxin and diphtheria antitoxin. Labeled to show the volume of each dose and the amount of L+ doses of toxin contained in each dose. Each 1 cc. represents 0.1 L+ dose of diphtheria toxin neutralized with a proper amount of diphtheria antitoxin.

The product should be used only if clear and free from sediment or flocculi.

The antitoxin used in diphtheria toxin-antitoxin mixture is produced from the horse, goat or sheep. Diphtheria toxin-antitoxin mixture has been largely supplanted by diphtheria toxoid.

*Actions, Uses and Dosage.*—Diphtheria toxin-antitoxin mixture is used for active immunization against diphtheria. It is employed chiefly for those who react severely to toxoid, principally older children and adults; ordinarily diphtheria toxoid is preferred. It is administered subcutaneously, preferably at the insertion of the deltoid, in three doses with an interval of one week between doses. A Schick test performed about six months after the last injection determines whether further immunization is necessary. In the presence of an outbreak of

diphtheria an immunizing dose of diphtheria antitoxin alone should be used if exposed children cannot be kept under regular medical observation.

### *Toxoids*

**DIPHTHERIA TOXOID-U. S. P.**—Anatoxin-Ramon.—Diphtheria Anatoxin.—“A sterile solution of the products of growth of the diphtheria bacillus (*Corynebacterium diphtheriae*) so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs but retaining the property of inducing active immunity. The toxicity of the Diphtheria Toxoid shall be so low that five times the initial dose for the adult human does not cause either local or general symptoms of diphtheria poisoning in a guinea pig within 30 days after its injection into the animal. The antigenic value shall be such that the initial dose for the human shall protect at least 80 per cent of guinea pigs, 6 weeks after injection, against five minimum lethal doses each of diphtheria test toxin. Diphtheria Toxoid complies with the requirements of the National Institute of Health of the United States Public Health Service.” U. S. P.

For description and regulations see the U. S. Pharmacopeia under Diphtheria Toxoid.

*Actions, Uses and Dosage.*—Diphtheria toxoid is used for active immunization against diphtheria. It is administered subcutaneously, preferably at the insertion of the deltoid, in two or three doses of 1 cc. each with an interval of three or four weeks between doses. Since some local and general reactions have been observed in adults and in children over 8 years of age, an intracutaneous test dose of 0.1 cc. of the toxoid diluted (1 in 20) with physiological saline solution should be given to determine sensitivity in such persons.

#### **CUTTER LABORATORIES**

**Diphtheria Toxoid:** 1 cc. and 30 cc. vials in packages of three 1 cc. vials, and one 30 cc. vial. Preserved with Merthiolate 1:10,000.

#### **LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.**

**Diphtheria Toxoid:** 1 cc. and 30 cc. vials in packages of three 1 cc. vials, and one 30 cc. vial. Each package is accompanied by a vial containing sufficient diluted diphtheria toxoid for ten sensitivity tests.

#### **ELI LILLY AND COMPANY**

**Diphtheria Toxoid:** 1 cc. and 30 cc. vials in packages of three 1 cc. vials, and one 30 cc. vial. Preserved with Merthiolate 1:10,000.

#### **NATIONAL DRUG COMPANY**

**Diphtheria Toxoid:** 3 cc. vials (one immunization) and 30 cc. vials. Preserved with Merthiolate 1:10,000.

## PARKE, DAVIS &amp; COMPANY

**Diphtheria Toxoid Plain:** 1 cc. and 30 cc. vials in packages containing three 1 cc. vials, and one 30 cc. vial.

## SHARP &amp; DOHME, INC.

**Diphtheria Toxoid:** Vials of 3 cc. (1 three-dose immunization) and 30 cc. (10 three-dose immunizations).

## E. R. SQUIBB &amp; SONS

**Diphtheria Toxoid:** 30 cc. vial in single packages. Preserved with Merthiolate 1:10,000.

**Diphtheria Toxoid for Reaction Test:** 1 cc. vial containing sufficient for ten tests.

## U. S. STANDARD PRODUCTS CO.

**Diphtheria Toxoid:** 1 cc., 6.0 cc., 20 cc. and 30 cc. vials in packages of two 1 cc. vials, one 6 cc. vial, one 20 cc. vial, and one 30 cc. vial.

## WYETH, INCORPORATED

**Diphtheria Toxoid:** 1 cc. and 30 cc. vials in packages of two and of twenty 1 cc. vials, and one 30 cc. vial. Each package is accompanied by a sufficient amount of diluted diphtheria toxoid for the reaction test.

**DIPHTHERIA TOXOID, ALUM PRECIPITATED-U. S. P.**—"A sterile suspension of diphtheria toxoid precipitated with alum from the solution in which the products of growth of the diphtheria bacillus (*Corynebacterium diphtheriae*) have developed and have been so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs but retain the property of inducing active immunity.

"Alum Precipitated Diphtheria Toxoid complies with the requirements of the National Institute of Health of the United States Public Health Service." *U. S. P.*

For description and regulations see the *U. S. Pharmacopeia* under Diphtheria Toxoid, Alum Precipitated.

**Actions, Uses and Dosage.**—Diphtheria toxoid, alum precipitated, is used for active immunization against diphtheria. It is administered subcutaneously, preferably at the insertion of the deltoid muscle. Because of the physical character of the product, absorption is delayed. Dosage: "Hypodermic, for active immunization, 1 cc. or 0.5 cc. (which ever is specified on the label) to be repeated once with an interval of 4 to 6 weeks." *U. S. P.*

## LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Refined Diphtheria Toxoid (Alum Precipitated):** 0.5 cc., 1 cc. and 5 cc. vials in packages of two 0.5 cc. vials; two 1 cc. vials, one 5 cc. vial and one 10 cc. vial. Preserved with Merthiolate 1:10,000.

**ELI LILLY AND COMPANY**

**Diphtheria Toxoid (Alum Precipitated):** In packages of two 0.5 cc. vials (one immunization) and 5 cc. vials (five immunizations).

**NATIONAL DRUG COMPANY**

**Diphtheria Toxoid (Alum Precipitated):** Toxoid adjusted to the 0.5 cc. dose in packages of one 0.5 cc. vial (supplementary dose), one 1 cc. vial (one 2-dose immunization), and one 5 cc. vial (five 2-dose immunizations). Preserved with Merthiolate 1:10,000.

**PARKE, DAVIS & COMPANY**

**Diphtheria Toxoid (Alum Precipitated Refined):** 1 cc., 2 cc. and 10 cc. vials containing one, two and ten doses, respectively. Preserved with Merthiolate 1:10,000.

**PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.**

**Diphtheria Toxoid (Alum Precipitated Refined):** Two 1 cc. vials (2 doses), and 10 cc. vials (10 doses). Preserved with 1:10,000 Merthiolate.

**SHARP & DOHME, INC.**

**Diphtheria Toxoid (Alum Precipitated, Refined):** Vials of 5 cc. (5 immunizations, two 0.5 cc. doses per immunization), 2 cc. (1 two-dose immunization) and 10 cc. (5 two-dose immunizations).

**E. R. SQUIBB & SONS**

**Refined Diphtheria Toxoid (Alum Precipitated):** 1 cc. vial in packages of two vials sufficient for one immunization, and 10 cc. vials for five immunizations. A more concentrated product is also available to be given preferably in injections of 0.5 cc. each, and 5.0 cc. vial sufficient for 5 immunizations. Preserved with Merthiolate 1:10,000.

**U. S. STANDARD PRODUCTS Co.**

**Diphtheria Toxoid (Alum Precipitated Refined):** 1 cc. and 10 cc. vials in packages of one and of ten 1 cc. vials, and one 10 cc. vial. Preserved with Merthiolate 1:10,000.

**WYETH, INCORPORATED**

**Diphtheria Toxoid, Alum Precipitated (Refined):** 0.5 cc., 1 cc., 5 cc. and 10 cc. vials in packages of one and of ten 0.5 cc. vials; one and ten 1 cc. vials; one 5 cc. vial, and one 10 cc. vial. Preserved with Merthiolate 1:10,000.

**DIPHTHERIA AND TETANUS TOXOIDS, ALUM PRECIPITATED-U. S. P.**—"Alum Precipitated Diphtheria and Tetanus Toxoids is a turbid, white, slightly gray or slightly pink suspension prepared by mixing suitable quantities of alum

precipitated diphtheria toxoid and alum precipitated tetanus toxoid, each of which possesses adequate potency to permit combining. The toxoids shall be mixed in such proportions that each cc., or less, of the combined toxoids will contain one individual human dose of each of the active ingredients. Alum Precipitated Diphtheria and Tetanus Toxoids complies with the requirements of the National Institute of Health of the United States Public Health Service." *U. S. P.*

For regulations, see the *U. S. Pharmacopeia* under Diphtheria and Tetanus Toxoids, Alum Precipitated.

**Actions, Uses and Dosage.**—Diphtheria and Tetanus Toxoids, Alum Precipitated, is used for active immunization against diphtheria and tetanus. It is administered subcutaneously, preferably at the insertion of the deltoid muscle. Because of the physical character of the product, absorption is delayed. The dosage is: "Hypodermic, for active immunization, 1 cc., to be repeated once with an interval of four to six weeks. Additional doses may be required to secure a negative Schick test." *U. S. P.*

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Combined Diphtheria-Tetanus Toxoids (Alum Precipitated Refined):** 1 cc. and 10 cc. vials in packages of two 1 cc. vials and of one 10 cc. vial.

ELI LILLY AND COMPANY

**Combined Diphtheria Toxoid-Tetanus Toxoid (Alum Precipitated):** 1 cc. and 10 cc. vials in packages of two 1 cc. vials (one immunization) and of one 10 cc. vial (five immunizations).

NATIONAL DRUG COMPANY

**Combined Diphtheria and Tetanus Toxoids (Alum Precipitated):** Two 0.5 cc. vials (one immunization) and two 2.5 cc. vials (five immunizations). Dosage: Two 0.5 cc. subcutaneous injections at four to six week intervals. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

PARKE, DAVIS & COMPANY

**Combined Diphtheria-Tetanus Toxoid:** Packages of three 2 cc. vials and packages of one 30 cc. vial.

**Combined Diphtheria-Tetanus Toxoid (Alum Precipitated):** 1 cc. vial. Preserved with 1:20,000 Phenol.

PITMAN-MOORE COMPANY

**Combined Diphtheria-Tetanus Toxoid (Alum Precipitated):** Packages of two 1 cc. vials and packages of one 10 cc. vial. Preserved with 1:10,000 Merthiolate.



SHARP & DOHME, INC.

**Combined Diphtheria-Tetanus Toxoid (Alum Precipitated):** 1 cc. and 10 cc. vials in packages of two 1 cc. vials and of one 10 cc. vial. Preserved with Merthiolate 1:10,000.

E. R. SQUIBB & SONS

**Combined Diphtheria Toxoid-Tetanus Toxoid (Alum Precipitated):** 1 cc. and 10 cc. vials in packages of two 1 cc. vials and of one 10 cc. vial.

WYETH, INCORPORATED

**Combined Diphtheria-Tetanus Toxoid (Alum Precipitated):** 1 cc. and 10 cc. vials in packages of two 1 cc. vials and of one 10 cc. vial.

**STAPHYLOCOCCUS TOXOID.**—*Staphylococcus* Anatoxin.—Univalent or polyvalent, potently hemolytic and dermonecrotic toxins of *Staphylococcus aureus* and *albus* altered by the formaldehyde-detoxifying process of Burnett (modified from Ramon). Antigenicity is maintained but toxicity is greatly diminished. The antigenic potency is determined by injecting 1 cc. of toxoid per kilogram intravenously into three rabbits and the resulting serum tested at the end of one and two weeks for its content of staphylococcus antitoxin. No staphylococcus toxoid is used which in doses of 0.2 cc. or less of the undiluted material will cause necrosis when injected into rabbits. The toxin is titrated to determine its dermonecrotic potency.

**Actions, Uses and Dosage.**—*Staphylococcus* toxoid has been reported a valuable agent in the prophylaxis and therapy of various staphylococcic pyodermas and localized pyogenic processes due to *Staphylococcus aureus* and *albus* (boil, carbuncle, furunculosis, acne, and so on). The toxoid is said to be effective in producing active immunity to the dermonecrotic and hemolytic elements of the toxins of *Staphylococcus aureus* and *albus*, irrespective of the individual strain of the infecting organism. The toxoid induces the production of staphylococcus antitoxin in the blood serum of immunized persons.

The initial dose should be not more than 0.1 cc. containing 10 skin necrotizing doses, injected subcutaneously at the insertion of the deltoid. Subsequent doses at weekly intervals should be increased by 10 to 20 skin necrotizing doses. Marked local, or a systemic reaction to any dose contraindicates increase of the succeeding dose.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Staphylococcus Toxoid:** Two 5 cc. vials, one containing toxoid derived from 100 necrotizing doses of toxin and one containing toxoid derived from 1,000 necrotizing doses of toxin.

NATIONAL DRUG COMPANY

**Staphylococcus Toxoid:** Two 5 cc. vials, one containing 100 necrotizing doses and one containing 1,000 necrotizing doses of toxin.

PARKE, DAVIS & COMPANY

**Staphylococcus Toxoid:** Two 5 cc. vials, one containing 100 necrotizing doses and one containing 1,000 necrotizing doses of toxin.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Staphylococcus Toxoid:** 5 cc. vials containing in each cubic centimeter the toxoid derived from 1,000 necrotizing doses of toxin. Preserved with 1:10,000 Merthiolate.

SHARP & DOHME, INC.

**Staphylococcus Toxoid:** Two 5 cc. vials, containing in each cubic centimeter the toxoid derived from 100 and 1,000 necrotizing doses of toxin, respectively. Preserved with Merthiolate 1:10,000.

**TETANUS TOXOID-U. S. P.**—"Tetanus Toxoid is a sterile solution of the product of growth of the tetanus bacillus (*Clostridium tetani*) so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs but retaining the property of inducing active immunity.

The toxicity of Tetanus Toxoid shall be so low that 5 cc. of the material does not cause any symptoms of tetanus in a guinea pig within a period of 21 days after its injection into the animal. The antigenic value shall be such that 1 cc. of the material shall 6 weeks after injection, protect at least 80 per cent of guinea pigs from all symptoms of tetanus for a period of 10 days after the injection of 10 minimum lethal doses of tetanus test toxin into each animal." U. S. P.

For description and regulations see the U. S. Pharmacopeia under Tetanus Toxoid.

**Actions, Uses and Dosage.**—To protect against infection, three doses of 1 cc. each intramuscularly or subcutaneously with an interval of three weeks between injections. An additional dose of 1 cc. should be given at the time of injury or infection. Active immunization of the tetanus would appear to be a desirable procedure in the case of individuals who are subject to a greater than normal hazard of the disease.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Tetanus Toxoid (Fluid):** 1 cc. and 30 cc. vials in packages of three 1 cc. vials and one 30 cc. vial.

**TETANUS TOXOID, ALUM PRECIPITATED-U. S. P.**—"A sterile suspension of tetanus toxoid, precipitated with alum from a solution in which the products of growth of the tetanus bacillus (*Clostridium tetani*) have developed and have been so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs, but retaining the property of inducing active immunity.

"Alum Precipitated Tetanus Toxoid complies with the requirements of the National Institute of Health of the United States Public Health Service."—*U. S. P.*

For description and regulations see the *U. S. Pharmacopeia* under Tetanus Toxoid, Alum Precipitated.

*Actions, Uses and Dosage.*—Tetanus toxoid is recommended for the production of active immunity to tetanus. The recommended human dose (1.0 cc. or 0.5 cc.) is injected subcutaneously, preferably in the region of the deltoid. Four to six weeks later the second and final injection is given. The immunity thus produced is reasonably persistent. However, it has been shown that, if some time after the original immunization a single injection of toxoid is given, there results a prompt (within two weeks) and marked rise in the antitoxic titer of the serum. Thus, in cases of injury to persons previously immunized, an injection of tetanus toxoid may suffice to protect against tetanus in place of the usual tetanus antitoxin. It should be borne in mind that in these cases several weeks is required, following the second injection of toxoid, before immunity may be assumed to be well established. Therefore, in any dubious instance the conservative course is the administration of antitoxin. Active immunization against tetanus would appear to be a desirable procedure in the case of individuals who are subject to a greater than normal hazard of the disease.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Tetanus Toxoid (Refined Alum Precipitated):** 1 cc. and 10 cc. vials in packages of two 1 cc. vials (two immunizing doses), and of one 10 cc. vial (ten immunizing doses). Preserved with Merthiolate 1:10,000.

ELI LILLY AND COMPANY

**Tetanus Toxoid (Alum Precipitated):** 0.5 cc. and 5 cc. vials in packages of two 1 cc. vials (two immunizing doses), and of one 5 cc. vial (ten immunizing doses). Preserved with Merthiolate 1:10,000.

NATIONAL DRUG COMPANY

**Tetanus Toxoid (Alum Precipitated):** Two 0.5 cc. vials (one immunization), one 5 cc. vial (five immunizations) and one 0.5 cc. vial for supplementary dose. Preserved with sodium ethylmercurithiosalicylate 1:10,000.

PARKE, DAVIS & COMPANY

**Tetanus Toxoid (Alum Precipitated Refined):** Two 1 cc. vials (one immunization treatment) and one 10 cc. vial (five immunization treatments).

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Tetanus Toxoid (Alum Precipitated):** 1 cc. vials in packages of two 1 cc. vials (two immunizing doses) and 10 cc. vial (ten immunizing doses). Preserved with Merthiolate 1:10,000.

SHARP & DOHME, INC.

**Tetanus Toxoid (Alum Precipitated Refined):** 1 cc. and 10 cc. vials in packages of two 1 cc. vials (one immunization) and of one 10 cc. vial (five immunizations). Preserved with Merthiolate 1:10,000.

E. R. SQUIBB & SONS

**Refined Tetanus Toxoid (Alum Precipitated):** 1 cc. vials in packages of two each (two immunizing doses); 10 cc. vials (ten immunizing doses). Preserved with Merthiolate 1:10,000.

WYETH, INCORPORATED

**Tetanus Toxoid (Alum Precipitated Refined):** 0.5 cc. and 1 cc. vials in packages of two 0.5 cc. vials (two immunizing doses) and of two 1 cc. vials (two immunizing doses); 5 cc. vial (five immunizing doses), 10 cc. vial (five immunizing doses) and 10 cc. vial (ten immunizing doses). Preserved with Merthiolate 1:10,000.

## Bacterial Vaccines

Bacterial vaccines, or bacterins, are suspensions of killed bacteria in physiological solution of sodium chloride, usually with the addition of some preservative such as cresol or phenol.

The dosage and intervals for bacterial vaccine treatment cannot be stated definitely. In general, the severer the disease, the smaller the dose should be; and the smaller the doses, the shorter the intervals. In mild affections no improvement may result until the vaccine is pushed to a systemic reaction.

Prophylactically, the typhoid and paratyphoid vaccines apparently have proved of great value as compared to other stock bacterial vaccines, the therapeutic use of which often rests on uncertain clinical evidence. Plague and cholera vaccines are also used in prophylaxis.

**BRUCELLA VACCINE.**—Undulant Fever Vaccine.—A bacterial vaccine obtained from *Brucella melitensis*, *Br. abortus* or *Br. suis*. No potency tests are made. Purity of cultures is determined by the study of colony formation, carbohydrate reactions and agglutination test with specific serum.

**Actions and Uses.**—Undulant fever vaccine is proposed for use in the treatment of undulant fever; its value is uncertain.

**Dosage.**—Subcutaneously or intramuscularly, 0.1 cc. to 0.25 cc. of the vaccine containing 2 to 6 billion killed organisms is used for the initial dose. Subsequent doses are gradually increased by the amount of the initial dose and may be administered at two to five day intervals until a dose of 1 cc. is reached. Further Vaccine should not be given to the patient, after a strong constitutional reaction has been obtained, until several weeks have elapsed in order to determine whether further treatment is required.

**JENSEN-SALSBERY LABORATORIES, INC.**

**Undulant Fever Vaccine:** 1 cc. vial. Each cc. contains 3 billion each of killed *Br. abortus* and *Br. suis*, in physiological solution of sodium chloride, preserved with 0.5 per cent of phenol.

**LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.**

**Undulant Fever Vaccine:** 5 cc. vial. Each cc. contains 1,000 million each of killed *Br. abortus* and *Br. suis*, in isotonic solution of sodium chloride, preserved with 0.5 per cent of phenol.

**NATIONAL DRUG COMPANY**

**Undulant Fever Vaccine (Abortus and Suis):** 30 cc. vials. Each cc. contains 2,500 million each of killed *Br. abortus* (bovine) and *Br. suis* (porcine), preserved with Merthiolate 1:10,000.

**PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.**

**Undulant Fever Vaccine (Abortus and Suis):** 5 cc. and 20 cc. diaphragm stoppered vials. Each cc. contains 1,000 million each of killed *Brucella abortus* and *Brucella suis*, preserved with Merthiolate 1:10,000.

**Undulant Fever Vaccine (Melitensis):** 5 cc. and 20 cc. diaphragm stoppered vials. Each cc. contains 2,000 million each of killed *Brucella melitensis*, preserved with Merthiolate 1:10,000.

**CHOLERA VACCINE-U. S. P.**—"A sterile suspension of killed cholera vibrios (*Vibrio comma*), of strains selected for high antigenic efficiency in isotonic sodium chloride solution or other suitable diluent. The vaccine shall contain, in each cc., at least 8,000 million cholera organisms. Cholera Vaccine complies with the requirements of the National Institute of Health of the United States Public Health Service." *U. S. P.*

**Actions, Uses and Dosage.**—This vaccine has been used for the prevention of cholera, administered in two or three doses. For the first two doses 0.5 cc. and for the third dose 1 cc. administered subcutaneously at intervals of seven to ten days. A stimulating dose of 1 cc. every six months while danger of infection exists has been suggested. However, the value of this vaccine has not been conclusively established.

**ELI LILLY AND COMPANY**

**Cholera Vaccine:** 20 cc. vial. Each cubic centimeter contains 8,000 million killed cholera vibrios.

**PERTUSSIS VACCINE.**—Whooping cough vaccine.—A sterile suspension of killed pertussis bacilli (*Hemophilus pertussis*) of one or more strains showing the characteristics of phase I as described by Leslie and Gardner. The suspension is

contained in isotonic solution of sodium chloride or other suitable diluent. The vaccine may be dispensed as a simple suspension, commonly known as "plain vaccine," or as an alum precipitated or aluminum hydroxide adsorbed suspension. The vaccine shall contain in each cubic centimeter not less than 10 billion organisms. The vaccine may be dispensed by itself or in combination with one or more other antigens, provided the combination does not lessen the antigenic value of the pertussis vaccine or otherwise make the product unsuitable for human use.

*Actions and Uses.*—Well controlled field studies indicate that pertussis vaccine possesses sufficient antigenic value to afford considerable protective value against whooping cough. The effect in lowering the death rate is even more striking than its effect in preventing an attack of the disease, since cases do occur in spite of the previous injection of vaccine, but such cases are usually less severe.

*Dosage.*—The most satisfactory dose has not been established adequately. In general, the vaccine when used as a plain vaccine should contain not less than 20 billion organisms per individual injection, with the total dose representing at least 60 billion, preferably much more. When used as precipitated vaccine the individual injection should contain not less than 10 billion organisms, with a total dose of 60 billion or more organisms. Pending more complete knowledge it is suggested that the user be guided by the dosage recommendation given on the manufacturer's product, since this represents the dosage accepted by the investigators whose methods have been used in preparing the vaccine.

#### CUTTER LABORATORIES

**Pertussis Vaccine (Phase I Concentrate):** 5 cc., 20 cc. and 50 cc. vials. *H. pertussis* 20,000 million per cc. Preserved with phenol 0.25 per cent and Merthiolate 0.002 to 0.005 per cent.

#### THE NATIONAL DRUG CO.

**Pertussis Vaccine (Double Strength):** 6 cc. vial (one immunization), 12 cc. vial (two immunizations) and 25 cc. vial (four immunizations). *H. pertussis* 20,000 million per cubic centimeter. Preserved with merthiolate 1:10,000.

#### PARKE, DAVIS & CO.

**Pertussis Vaccine (Immunizing Sauer):** 6 cc. and 24 cc. vials. 15,000 million *H. pertussis* per cubic centimeter.

#### SHARP & DOHME, INC.

**Pertussis Bacterin ("H" Strength):** 5 cc. and 20 cc. vials. 20,000 million *H. pertussis* per cubic centimeter. Preserved with phenol 0.5 per cent.

#### E. R. SQUIBB & SONS

**Pertussis Vaccine (Single Strength):** 8 cc. and 24 cc. vials. 10,000 million *H. pertussis* per cubic centimeter. Preserved with phenol 0.5 per cent.

**Pertussis Vaccine (Double Strength):** 5 cc. and 20 cc. vials. 20,000 million *H. pertussis* per cubic centimeter. Preserved with phenol 0.5 per cent.

THE UPJOHN COMPANY

**Pertussis Vaccine (Single Strength):** 24 cc. vials. 10,000 million *H. pertussis* per cubic centimeter. Preserved with phenol 0.5 per cent.

**Pertussis Vaccine (Double Strength):** 5 cc. and 20 cc. vials. 20,000 million *H. pertussis* per cubic centimeter. Preserved with phenol 0.5 per cent.

WYETH INCORPORATED

**Pertussis Vaccine:** 12 cc. and 20 cc. vials. 15,000 million *H. pertussis* per cubic centimeter. Preserved with phenol 0.5 per cent.

**PERTUSSIS VACCINE ALUM PRECIPITATED.—**

A bacterial vaccine prepared from alum precipitated, killed *H. pertussis*.

*Actions and Uses.*—Same as Bacterial Vaccine made from *H. pertussis*.

*Dosage.*—Three 1 cc. subcutaneous injections of 10,000 million or 15,000 million *H. pertussis* at three to four week intervals.

THE NATIONAL DRUG CO.

**Pertussis Vaccine (Alum Precipitated):** One 0.5 cc. vial (supplementary dose). *H. Pertussis* 30,000 million per cc. Preserved with merthiolate 1:10,000. For use as a booster dose to maintain a high protective level. It is desirable to give a booster dose (0.5 cc.) one year after primary immunization and again at school age.

PARKE, DAVIS & CO.

**Pertussis Vaccine (Alum Precipitated Sauer):** 1.5 cc. and 6 cc. vials. Each cubic centimeter contains 30,000 million *H. pertussis* in 0.6 per cent solution of sodium chloride. Preserved with merthiolate, 0.01 per cent.

THE UPJOHN COMPANY

**Pertussis Vaccine (Alum Precipitated):** 3 cc. vials (one immunization) and 10 cc. vials (three immunizations). 10,000 million *H. pertussis* per cc. Preserved with phenol 0.5 per cent.

**PERTUSSIS VACCINE AND ANTITOXIN, COMBINED.**—**Pertussis Endotoxoid-Vaccine.**—A suspension of *Hemophilus pertussis*, phase I organisms, in a solution of *H. pertussis* endotoxoid. The bacterial suspension is prepared after the technic of Kendrick and Eldering, and the endotoxoid by the Strean method.

*Actions and Uses.*—Pertussis endotoxoid-vaccine is recommended for the active immunization of individuals who are susceptible to pertussis. It is not intended for treatment of the disease or for the production of immunity once exposure has taken place.

*Dosage.*—For children 4 years of age and older a total amount of 6 cc. should be administered subcutaneously in four doses twelve to fourteen days apart as follows: 1 cc., 1.5 cc., 1.5 cc., 2 cc. For children under 4 years of age the dose may be reduced for the initial injection; a satisfactory dosage schedule consists of five injections, also at twelve to fourteen day intervals, as follows: 0.5 cc., 1 cc., 1 cc., 1.5 cc., 1.5 cc. After completion of the preliminary course it is customary to give a fortifying dose of 2 cc. (one injection) each year up to 5 years of age. When it is inconvenient to have the patient return for injections more than three times, three injections can be given at twelve to fourteen day intervals, as follows: 1 cc., 2 cc., 2 cc. Dosage intervals of one month may be preferred in cases in which the additional length of time required for vaccination is not objectionable.

**PERTUSSIS VACCINE AND ANTITOXIN COMBINED WITH DIPHTHERIA TOXOID.**—Pertussis Endotoxoid Vaccine with Diphtheria Toxoid.—A suspension of pertussis vaccine in a solution of pertussis antitoxin, made from *Hemophilus pertussis* phase I organisms combined with diphtheria toxoid. The bacterial suspension is prepared after the technic of Kendrick and Eldering, the bacterial solution by the Stroom method, and the diphtheria toxoid is standardized in accordance with the requirements of the National Institute of Health.

*Actions and Uses.*—For active immunization against pertussis and diphtheria. It is not intended for treatment or for the production of immunity once exposure has taken place.

*Dosage.*—See under Pertussis Vaccine and Antitoxin Combined and under Diphtheria Toxoid.

AYERST, McKENNA & HARRISON, LTD.

**Pertussis Endotoxoid-Vaccine with Diphtheria Toxoid:** 10 cc. vials. Each cc. contains 25 billions of *H. pertussis* organisms and antigen derived from approximately 25 billion *H. pertussis* organisms, together with one immunizing dose of diphtheria toxoid. Preserved with Merthiolate 1:10,000.

**PERTUSSIS VACCINE COMBINED WITH DIPHTHERIA TOXOID.**—A combination of pertussis vaccine with diphtheria toxoid.

*Actions and Uses.*—Employed in the simultaneous immunization of susceptible persons against diphtheria and whooping cough.

*Dosage.*—Three doses of 1 cc. at three to four week intervals.



## THE NATIONAL DRUG CO.

**Diphtheria Toxoid, Alum Precipitated and Pertussis Vaccine Combined:** Three 0.5 cc. vials (one immunization) and three 2.5 cc. vials (five immunizations). 30,000 million *H. pertussis* per cc. with diphtheria toxoid. Dosage: Three 0.5 cc. subcutaneous injections at four to six week intervals. Preserved with Merthiolate 1:10,000.

## PARKE, DAVIS &amp; Co.

**Diphtheria Toxoid-Pertussis Vaccine Mixed (Sauer):** 6 cc. vials (one immunization) and 24 cc. vials (four immunizations). Each cubic centimeter contains 15,000 million *H. pertussis* and 0.5 cc. diphtheria toxoid.

## SHARP &amp; DOHME, INC.

**Diphtheria-Pertussis Antigens Combined (Alum Precipitated):** 10 cc. vials (three dose immunizations). 10,000 million *H. pertussis* diphtheria toxoid immunizing dose. Preserved with phenol 1:50,000.

## THE UPJOHN COMPANY

**Pertussis Vaccine, Diphtheria Toxoid, Combined, Alum Precipitated:** 3 cc. vials (one immunization) and 10 cc. vials (three immunizations). 10,000 million *H. pertussis* per cubic centimeter. Preserved with Merthiolate 1:10,000.

**PERTUSSIS VACCINE COMBINED WITH DIPHTHERIA AND TETANUS TOXOIDS.**—A combination of pertussis vaccine with diphtheria toxoid and tetanus toxoids.

*Actions and Uses.*—Employed in the simultaneous immunization of susceptible persons against whooping cough, diphtheria and tetanus.

*Dosage.*—Three subcutaneous injections of 1 cc. at three to four week intervals.

## THE NATIONAL DRUG CO.

**Diphtheria-Tetanus-Pertussis Combined Vaccine (Alum Precipitated):** Three 1 cc. vials (one immunization) and three 5 cc. vials (five immunizations). 10,000 million *H. pertussis*, diphtheria toxoid and tetanus toxoid, 0.33 cc. each, per cubic centimeter. Preserved with Merthiolate 1:10,000.

## SHARP &amp; DOHME, INC.

**Diphtheria-Tetanus-Pertussis Antigens Combined (Alum Precipitated):** One 3 cc. vial (one 3 dose immunization) and one 10 cc. vial (three 3 dose immunizations). 10,000 million *H. pertussis* per cubic centimeter with diphtheria toxoid and tetanus toxoid. Preserved with Merthiolate 1:10,000.

E. R. SQUIBB & SONS

**Diphtheria and Tetanus Toxoid Alum Precipitated and Pertussis Vaccine Combined:** 1.5 cc. (one 3 dose immunization) and 7.5 cc. vials (five 3 dose immunizations). Preserved with sodium ethylmercurithiosalicylate 1:10,000.

**PLAGUE VACCINE-U. S. P.**—"A sterile suspension of killed plague bacilli (*Pasteurella pestis*), of a strain selected for high antigenic efficiency in isotonic solution of sodium chloride or other suitable diluent. The vaccine shall contain, in each cc. at least 2,000 million plague organisms. Plague Vaccine complies with the requirements of the National Institute of Health of the United States Public Health Service." *U. S. P.*

**Actions and Uses.**—This vaccine has been used for the prevention of plague. The value of this vaccine is very doubtful.

**Dosage.**—"Hypodermic, for active immunization, 0.5 cc. and 1 cc. with a 7 to 10 day interval, the latter dose preferably to be repeated once." *U. S. P.*

CUTTER LABORATORIES

**Plague Vaccine:** 20 cc. vials containing 2,000 million killed bacilli.

**SMALLPOX VACCINE.**—Glycerinated Vaccine Virus.—Jennerian Vaccine.—Antismallpox Vaccine.—"Smallpox Vaccine consists of a glycerinated suspension of the vesicles of vaccinia or cowpox which have been obtained from healthy vaccinated animals of the bovine family. The vesicles must be removed and the vaccine must be prepared under aseptic conditions.

The vesicles must be removed from the animal at the time of suitable development, thoroughly triturated and made into a smooth suspension with an aqueous solution of glycerin. This solution must not be acid to bromocresol purple T. S. and not distinctly alkaline to phenol red T. S. Smallpox vaccine complies with the requirements of the National Institute of Health of the United States Public Health Service." *U. S. P.*

**Actions and Uses.**—Smallpox vaccine acts by rendering the vaccinated person resistant to invasion by the virus of smallpox and is used in the prevention of that disease. The vaccine is administered by cutaneous insertion, preferably in the deltoid region, with a sterile needle which is held parallel to the cleansed skin and depressed quickly, breaking the epithelium, about 30 times through a drop of the vaccine. No dressing is to be employed.

**STAPHYLOCOCCUS VACCINE.**—Made from *Staphylococcus aureus*, from *Staphylococcus albus*, or from *Staphylococcus citreus*, or from all three.

**Actions and Uses.**—Staphylococcus vaccine is used in carbuncles, furunculosis, sycosis, and certain cases of acne. An

autogenous vaccine is preferable, but if this cannot be made, a stock vaccine can be used with some prospect of success. The forms of acne most likely to respond are characterized by deep-seated pustules, with considerable induration, occurring on the face, chest and back. When the lesions are superficial and indolent, the acne bacillus vaccine may give good results.

*Dosage.*—100 million to 1,000 million killed bacteria.

ELI LILLY AND COMPANY

**Staphylococcus Vaccine:** 5 cc. vials. Each cc. contains 2,000 million each of killed *Staphylococcus aureus* and *Staphylococcus albus*, in isotonic solution of sodium chloride, preserved with 1:10,000 Merthiolate.

**Staphylococcus Aureus Vaccine:** 5 cc. vials. Each cc. contains 2,000 million killed *Staphylococcus aureus*. Preserved with 1:10,000 Merthiolate.

PARKE, DAVIS & COMPANY

**Furunculosis Vaccine:** 5 cc. and 20 cc. vials. Each cc. contains 2,000 million killed *Staphylococcus aureus*.

**TYPHOID VACCINE-U. S. P.**—"A sterile suspension in isotonic sodium chloride solution or other suitable diluent of killed typhoid bacilli (*Eberthella typhosa*), of a strain selected for high antigenic efficiency. The vaccine shall contain, in each cc., at least 1,000,000,000 typhoid organisms. Typhoid Vaccine complies with the requirements of the National Institute of Health of the United States Public Health Service." *U. S. P.*

For description and standards see the *U. S. Pharmacopeia* under Typhoid Vaccine.

*Actions and Uses.*—Typhoid vaccine is of considerable value in the prevention of typhoid fever. Typhoid vaccine is also used in nonspecific protein therapy, but such use is sometimes attended by dangerous and even fatal reactions.

*Dosage.*—"Average Dose—Hypodermic, for active immunization 0.5 cc. and 1 cc., the latter dose to be repeated once."—*U. S. P.* As a preventive, typhoid vaccine should be administered only to healthy persons. The skin should be sterilized with iodine and an initial dose of 500 million bacteria injected, with aseptic precautions. This injection should be followed in from seven to ten days by a second dose of one billion bacteria and a third injection of the same size is given from seven to ten days after the second.

CUTTER LABORATORIES

**Typhoid Vaccine (Prophylactic):** 1 cc. bottles in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (strain 58, the Panama carrier strain). Preserved with 0.25 per cent tricresol.

## ELI LILLY AND COMPANY

**Typhoid Vaccine (Prophylactic):** 1 cc. vials in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (strain 58, the Panama carrier strain). Preserved with 1:10,000 Merthiolate.

## NATIONAL DRUG COMPANY

**Typhoid Vaccine:** 1 cc. vials in packages of three, one containing 1,000 million and two each containing 2,000 million killed bacilli (strain 58, the Panama carrier strain); 5 cc. vials containing 2,000 million killed bacilli of the same strain per cubic centimeter. Preserved with Merthiolate 1:10,000.

## PARKE, DAVIS &amp; COMPANY

**Typhoid Vaccine:** 1 cc. vials in packages of three, one containing 500 million and two each containing 1,000 million killed typhoid bacilli Panama carrier strain 58.

**Typhoid Vaccine:** 5 cc. and 20 cc. vials containing 1,000 million killed typhoid bacilli Panama strain 58 per cubic centimeter.

## PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Typhoid Vaccine:** 5 cc. and 20 cc. vials. Each cc. contains 1,000 million killed typhoid bacilli (Panama carrier strain 58.) Preserved with sodium ethyl mercuri thiosalicylate 1:10,000.

## U. S. STANDARD PRODUCTS Co.

**Typhoid Vaccine:** 1 cc. vials in packages of three, one containing 500 million and two each containing 1,000 million killed bacilli (strain 58, the Panama carrier strain); 5 cc. and 20 cc. vials containing 1,000 million killed bacilli of the same strain per cubic centimeter. Preserved with 0.5 per cent of phenol.

## Toxoid-Vaccine Mixtures

**STAPHYLOCOCCUS TOXOID-VACCINE MIXTURE.**—A mixture containing in each cubic centimeter 2,000 million killed *Staphylococcus aureus* and the staphylococcus toxoid derived from 1,000 necrotizing doses of toxin.

*Actions and Uses.*—*Staphylococcus* toxoid-vaccine mixture is used in infections of recognized staphylococcic etiology. Such a mixture has been offered to neutralize the toxin and effect lysis of the invading organism. Local reactions may follow injection.

*Dosage.*—Ten doses, the first dose being 0.1 cc. (200 million *Staphylococcus aureus*, staphylococcus toxoid 100 necrotizing doses), the tenth 1.0 cc. Each dose is increased by 0.1 cc. The agent is given subcutaneously at weekly intervals.

THE NATIONAL DRUG CO.

**Vatox Staphylococcus Toxoid-Vaccine:** 6 cc. vials. Preserved with Merthiolate 1:10,000.

## Diagnostic Agents

### TOXINS FOR IMMUNITY TESTS

**DIPHTHERIA TOXIN, DIAGNOSTIC-U. S. P.**—Diphtheria toxin for the Schick Test.—“A sterile solution of the toxic products of growth of the diphtheria bacillus (*Corynebacterium diphtheriae*). It complies with the requirements of the National Institute of Health of the United States Public Health Service.” *U. S. P.*

For description and regulations see the *U. S. Pharmacopeia* under Diphtheria Toxin Diagnostic.

**Actions and Uses.**—This test is intended to determine those persons who are immune to diphtheria. In nonimmune persons a circumscribed area of redness and infiltration from 1 to 2 cm. in diameter develops at the site following injection of 0.1 cc. of the Schick test material representing  $\frac{1}{50}$  M. L. D. of diphtheria toxin. The reaction occurs in from twenty-four to forty-eight hours, and is at its height in from forty-eight to seventy-two hours. It remains for from six to twelve days, is followed by slight scaling, and leaves a brownish, pigmented spot. In some persons, a pseudoreaction may occur, which may be differentiated by its earlier appearance and disappearance, and the fact that it is less circumscribed and is not followed by pigmentation.

Diphtheria toxin diluted for use with isotonic solution of sodium chloride soon loses potency so that the material should be diluted only on the day of test. Diphtheria toxin diluted with peptone solution and certain other agents, especially boric acid and borates or human albumin, is apparently quite stable.

**Dosage.**—“Intracutaneous, for determining susceptibility (Schick Test), 0.1 cc. of the dilution, representing one-fiftieth of the minimum lethal dose.” *U. S. P.*

### CUTTER LABORATORIES

**Diphtheria Toxin for the Schick Test (Diluted):** 1 cc. vial containing sufficient diluted toxin for 10 tests. Preserved with 0.5 per cent phenol.

### LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Diphtheria Toxin for Schick Test (in Peptone Solution):** 1 cc. and 5 cc. vials, containing sufficient diluted toxin for 10 and 50 tests, respectively; also in the form of heat treated peptone-diluted toxin in a package containing sufficient material for 10 control tests respectively.

### ELI LILLY AND COMPANY

**Diphtheria Toxin for Schick Test (Diluted):** 1 cc. and 10 cc. vials containing sufficient diluted toxin for 10 and 100

tests, respectively, in isotonic solution of sodium chloride containing 0.1 per cent gelatin.

**NATIONAL DRUG COMPANY**

**Diphtheria Toxin for Schick Test (Diluted):** 10 cc. vials containing sufficient diluted toxin for 10, 50 and 100 tests. Preserved with Merthiolate 1:10,000.

**PARKE, DAVIS & COMPANY**

**Diphtheria Toxin for Schick Test (Diluted):** 1 cc., 5 cc. and 10 cc. vials containing sufficient diluted toxin for 10, 50 and 100 tests, respectively; also supplied in the form of heat treated diluted toxin for control tests.

**PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.**

**Diphtheria Toxin for the Schick Test:** 1 cc. vial containing sufficient diluted toxin for 10 tests. Preserved with 0.5 per cent phenol.

**SHARP & DOHME, INC.**

**Diphtheria Toxin for the Schick Test (Diluted):** 1 cc., 5 cc. and 10 cc. vials containing sufficient diluted toxin for 10, 50 and 100 tests, respectively; also supplied in the form of heat treated diluted toxin in 5 cc. vial containing sufficient material for 50 control tests.

**E. R. SQUIBB & SONS**

**Diphtheria Toxin for the Schick Test (In Peptone Solution):** 1 cc. vials containing sufficient diluted toxin for 10 tests, preserved with 0.5 per cent of phenol.

**WYETH, INCORPORATED**

**Diphtheria Toxin for the Schick Test (Diluted):** 1 cc., 2.5 cc. and 5 cc. vials containing sufficient diluted toxin for 10, 25 and 50 tests, respectively; also in the form of heat treated diluted toxin in vials containing sufficient material for 10, 25 and 50 control tests, respectively.

**SCARLET FEVER STREPTOCOCCUS TOXIN FOR DICK TEST.**—For definition see this title under Bacterial Toxins.

*Actions and Uses.*—The toxin of the hemolytic streptococcus of scarlet fever is used for determination of susceptibility to scarlet fever and for immunization against scarlet fever. The toxin is first carefully standardized on human beings and diluted so that 0.1 cc. represents a skin test dose.

The test dose is injected intracutaneously on the forearm and the degree of susceptibility is determined at the end of from twenty-two to twenty-four hours. An area of reddening 1 cm. or more in diameter constitutes some degree of a positive reaction while a smaller area of reddening is considered negative.

Reactions which have appeared but which have entirely faded at the end of twenty-four hours are regarded as negative. Positive reactions fade rapidly and have usually disappeared at the end of from forty-eight to seventy-two hours.

Scarlet fever streptococcus toxin diluted for use will retain its potency for at least two months at room temperature.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Scarlet Fever Streptococcus Toxin for the Dick Test:**  
2 cc. and 10 cc. vials containing sufficient diluted toxin for withdrawal to perform 5 and 50 tests, respectively. Preserved with 0.4 per cent phenol.

NATIONAL DRUG COMPANY

**Scarlet Fever Streptococcus Toxin for the Dick Test:**  
2 cc. and 11 cc. vials containing sufficient diluted toxin for withdrawal to perform 5 and 50 tests, respectively. Preserved with 0.4 per cent phenol.

PARKE, DAVIS & COMPANY

**Scarlet Fever Streptococcus Toxin for the Dick Test:**  
2 cc. vials containing sufficient diluted toxin for withdrawal to perform 5 tests.

**Scarlet Fever Streptococcus Toxin for the Dick Test:**  
10 cc. vial containing sufficient diluted toxin for withdrawal to perform 50 tests.

SHARP & DOHME, INC.

**Scarlet Fever Streptococcus Toxin for the Dick Test:**  
2 cc. ampuls containing sufficient diluted toxin for withdrawal to perform 5 tests.

**Scarlet Fever Streptococcus Toxin for the Dick Test:**  
10 cc. vial containing sufficient diluted toxin for withdrawal to perform 50 tests.

E. R. SQUIBB & SONS

**Scarlet Fever Streptococcus Toxin for the Dick Test:**  
2 cc. and 11 cc. vials containing sufficient diluted toxin for withdrawal to perform 5 and 50 tests, respectively. Preserved with 0.3 per cent of phenol.

U. S. STANDARD PRODUCTS Co.

**Scarlet Fever Streptococcus Toxin for the Dick Test:**  
2 cc. ampules containing sufficient diluted toxin for withdrawal to perform 5 tests and 11 cc. vial ampuls containing sufficient diluted toxin for withdrawal to perform 50 tests. Preserved with phenol 0.4 per cent.

WYETH, INCORPORATED

**Scarlet Fever Streptococcus Toxin for the Dick Test:**  
2 cc. and 10 cc. vials containing sufficient diluted toxin for

withdrawal to perform five and fifty tests, respectively. Preserved with 0.4 per cent phenol.

**SCARLET FEVER STREPTOCOCCUS ANTITOXIN FOR SCHULTZ-CHARLTON TEST.**—(For definition and descriptions of scarlet fever streptococcus antitoxin see this title under Antitoxins.)

*Actions and Uses.*—The antitoxic serum of the hemolytic streptococcus of scarlet fever which is used to produce temporary passive immunity and in the treatment of the disease is also used in the performance of a skin test to differentiate the rash of scarlet fever from eruptions due to other causes. When doubt exists as to the nature of the eruption in cases where a diagnosis of scarlet fever cannot otherwise be ruled out, a small dose of not more than 0.2 cc. (containing 2,000 to 5,000 original neutralizing units) of the antitoxin is injected intracutaneously in the exanthematous area for the test. A positive reaction is known as the Schultz-Charlton phenomenon and consists in the more or less complete disappearance of the rash over an area of 2 cm. or more in diameter at the site of injection within four to twenty-four hours. This reaction is of significance because only scarlet fever immune serum is specific against the toxin responsible for the rash in this disease. Fading or blanching of the rash at the site of injection of scarlet fever antitoxin is, therefore, the result of local neutralization of the toxin of this disease. The reaction usually remains evident for several days or until the rash in general has begun to fade.

**TUBERCULINS.**—Many different methods have been used to prepare from the tubercle bacillus (*Mycobacterium tuberculosis*) substances which might be used in the diagnosis or treatment of tuberculosis. These have been, in general, called tuberculins, and a few of the more prominent are enumerated here. For diagnosis, either Koch's old tuberculin or a preparation from the filtrate of a synthetic nonprotein culture medium in which tubercle bacilli have been grown, is usually employed. For treatment, each tuberculin has its advocates, but it is doubtful whether there is any essential difference in the action of the various forms. The strength varies, however, not only in tuberculins prepared by different methods, but also in different batches prepared in exactly the same manner. A tuberculin, designated Purified Protein Derivative, has been prepared within the last few years and is now extensively employed.

Tuberculin has a wide use in the diagnosis of tuberculous infection. A positive reaction to tuberculin indicates that infection with the tubercle bacillus has occurred. The great majority of people who have been infected by tubercle bacilli react to tuberculin, so that the tuberculin test is a valuable procedure in epidemiological investigations. However, a small proportion of people who have been infected do not react, and this fact must be taken into account in epidemiological studies. Patients with far advanced or rapidly progressive disease may not react, and,



on the other hand, persons who have made a complete recovery from slight tuberculous infection may also be negative to tuberculin; also in the presence of febrile disease, as in measles, the capacity to react may be temporarily abolished.

Tuberculin has its widest usage at the present time in tuberculosis case-finding. Its use is based on the assumption that practically all persons with clinical tuberculosis react to tuberculin. The tuberculin test is cheaper than roentgenological examination with standard size film and therefore if it is negative is a measure of economy, obviating the necessity of the most costly examination.

In cases of pulmonary or glandular disease of obscure etiology, particularly in children, the tuberculin test is of value, for in such cases, within the limitations set in the preceding paragraph, failure to react to tuberculin excludes tuberculosis in the diagnosis.

In recent years the use of tuberculin in the treatment of tuberculosis has declined greatly. At present tuberculin is more commonly employed in the treatment of nonpulmonary than pulmonary tuberculosis, although individual practice varies, and a few physicians use this form of therapy routinely in pulmonary cases. Treatment is generally carried out by beginning with a small dose, not large enough to cause any constitutional disturbance, and increasing the dosage gradually in injections at intervals of a few days or weeks. Ordinarily old tuberculin is employed, but the other preparations listed in the following paragraphs are used occasionally. The tuberculin treatment is not a true form of immunization. The basis for treatment lies, first, in the fact that the substance, properly used, causes a mild focal reaction at the site of infection leading gradually to fibrosis, and, second, in the fact that frequently repeated injection gradually desensitizes the body temporarily. Desensitization to tuberculin is believed to prevent destructive reactions when spread of tubercle bacilli occurs in the body.

*Danger from Tuberculins.*—The early history of the therapeutic use of tuberculin is full of instances showing that it may be a dangerous substance. The great risk lies in the chance of a severe reaction, and every precaution should be taken in treatment, not to underestimate the patient's susceptibility to the tuberculin. This susceptibility varies enormously in different individuals and at different stages of the treatment, entirely out of relation to the progress of the disease. The use of tuberculin in treatment therefore requires special knowledge and experience. The doses ordinarily used in diagnosis rarely lead to constitutional reaction.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Tuberculin (Diagnostic):** Packages containing three 1 cc. diaphragm stoppered vials of tuberculin, one of each dilution

1:100, 1:1,000 and 1:10,000. Preserved with 0.5 per cent phenol.

**PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN-U. S. P.**—"A sterile, soluble product of the growth of tubercle bacillus (*Mycobacterium tuberculosis*) prepared in a special liquid free from protein. Purified Protein Derivative of Tuberculin complies with the requirements of the National Institute of Health of the United States Public Health Service." *U. S. P.*

For description and regulations see the U. S. Pharmacopeia under Tuberculin, Purified Protein Derivative.

The method of administration is the Mantoux test described under the heading Old Tuberculin. Intracutaneous injection is made, as with old tuberculin, but instead of the doses given for old tuberculin, standard doses of 0.00002 mg. and 0.005 mg. of purified protein derivative of tuberculin are employed. The method of reading reactions is the same as that given in the section on old tuberculin.

PARKE, DAVIS & COMPANY

**Tablets Tuberculin, Purified Protein Derivative (First Strength):** Packages containing 2 vials (5 tests each) and 1 cc. vial of sterile diluent; and packages containing 10 tablets (100 tests) with 10 cc. vial of diluent.

**Tablets Tuberculin, Purified Protein Derivative (Second Strength):** Packages containing 2 vials (5 tests each) and 1 cc. of sterile diluent; and packages containing 10 tablets (100 tests) with 10 cc. vial of diluent.

**Tablets Tuberculin, Purified Protein Derivative (First and Second Strength):** Sufficient for 20 tests each of first and second strength. Packages for individual testing containing 2 vials, 1 tablet each of first strength and 2 vials, 1 tablet each of second strength with a 5 cc. vial of sterile diluent.

**OLD TUBERCULIN-U. S. P.**—Tuberculin-Koch.—Concentrated Tuberculin.—Crude Tuberculin.—"A sterile solution in a special liquid culture medium of the soluble products of growth of the tubercle bacillus (*Mycobacterium tuberculosis*) and should contain about 50 per cent of glycerin. Old Tuberculin complies with the requirements of the National Institute of Health of the United States Public Health Service." *U. S. P.*

For description and standards see the U. S. Pharmacopeia under Tuberculin, Old.

**Actions and Uses.**—For diagnosis, old tuberculin is used most commonly by intracutaneous injection (Mantoux test) or cutaneously by application to a scarified spot on the skin (von Pirquet test). It may also be used in the form of an ointment or paste applied directly (Moro test) or through the medium of an absorbent material or patch (patch test). The latter method has gained in popularity in recent years. Inflammation at the

site of application is evidence that at some time the patient has been infected with tubercle bacilli. In such cases the reaction is called "positive."

The intracutaneous (Mantoux) test is most commonly employed. Concentrated old tuberculin is diluted, under sterile precautions, so that 0.1 cc. (the quantity to be injected) will contain 0.01 cmm. of old tuberculin (commonly but erroneously called 0.01 mg.). Dilution of the tuberculin should be made on the day of test.

The diluted material should be injected intracutaneously into the skin of the flexor surface of the forearm. A 1 cc. tuberculin syringe and a sharp 26 gauge one-half inch needle are used.

The reactions are read 48 to 72 hours after injection. In ordinary practice, if the reaction is negative following a dose of 0.01 cmm., a second dose of 1.0 cmm. is injected into the opposite forearm. Occasionally, for extra precaution, an intermediate dose of 0.1 cmm. is employed and sometimes this dose only is used. The latter practice saves time, but occasionally moderately severe reactions may occur, and it is generally recognized that a number of persons who would be positive to 1.0 cmm. do not react to 0.1 cmm. In the absence of a reaction following the last dose of tuberculin, the patient is regarded as negative. The reaction consists in a papule of edema 5 mm. in diameter with a surrounding zone of redness at the point of the tuberculin injection. If there is no edema or induration, the reaction should be considered negative. This reaction ordinarily reaches its height in forty-eight hours.

For treatment, from one one hundred-millionth (0.00000001) to one millionth (0.000001) cc. may be used as the initial dose, and not more than two doses a week should be given.

The patch test, a modification of the Moro percutaneous test, may be used for infants and children wherever there is objection to the use of the needle a strip of adhesive tape, on which has been placed two 1 cm. squares of filter paper saturated with tuberculin and one 1-cm. square of filter paper as a control [dried] is affixed in contact with the skin after cleaning with acetone or ether. The patch test must be kept dry and the adhesive must remain in close contact with the skin for 48 hours, after which it is removed. The test is read 48 hours later, that is, 96 hours after the tape was first put on. A positive reaction consists of a sharply circumscribed, reddened, and infiltrated area with follicular elevations. The patch test is roughly equivalent to the first strength (0.01 cmm.) of old tuberculin intracutaneously. Therefore, if negative, a second test with 0.1 cmm. or 1.0 cmm. of old tuberculin may be performed by intracutaneous injection.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Intracutaneous Tuberculin for the Mantoux Test:**  
Vial containing old tuberculin supplied with a vial containing isotonic solution of sodium chloride sufficient to make 1 cc.

containing 1 mg. of tuberculin. Preserved with 50 per cent glycerin.

**Tuberculin Old (Koch's):** 1 cc. container of tuberculin.

**Tuberculin Patch Test (Vollmer):** Cellophane wrapped, assembled adhesive strip having two test squares and one control square each of filter paper saturated with concentrated old tuberculin and concentrated uninoculated broth, respectively. Supplied in packages containing 1 test, 10 tests and 100 tests.

**ELI LILLY AND COMPANY**

**Old Tuberculin, Human Strain Concentrated:** 1 cc. vials containing 1 Gm. of tuberculin or containing a stated amount of concentrated tuberculin for making dilutions containing from 0.001 mg. to 100 mg. per cubic centimeter, each packaged with a vial of physiological solution of sodium chloride for making serial dilutions.

**PARKE, DAVIS & COMPANY**

**Tuberculin Old (Koch):** 1 cc. vials; preserved with 50 per cent of glycerin.

**Tuberculin Old for the von Pirquet Test:** Sealed tubes in packages of three, each tube containing tuberculin sufficient for one test, accompanied by three tubes of bouillon for control; preserved with 50 per cent of glycerin.

**Tuberculin for the Mantoux Test:** 1 cc. vial containing 0.001 cc. of Tuberculin Old (Koch) packaged with a 1 cc. vial of diluent (sufficient for 10 tests); 10 cc. vial containing 0.01 cc. of Tuberculin Old (Koch) packaged with a 10 cc. vial of diluent (sufficient for 100 tests). A filtrate from bouillon cultures from both human and bovine preserved with 50 per cent glycerin.

**NEW TUBERCULIN, B. E.—Bazillenemulsion, Koch.—Bacilli Emulsion.**—Bacilli emulsion is practically a bacterial vaccine. It is made by suspending one part of pulverized tubercle bacilli. *Mycobacterium tuberculosis*, in 100 parts of distilled water and 100 parts of glycerin. One cc. thus corresponds to 5 mg. of tubercle bacilli.

It is a white, fairly permanent emulsion, but should be shaken thoroughly before making dilutions. New tuberculin, B. E., is occasionally used in the treatment of tuberculosis.

**NEW TUBERCULIN B. E. DRIED.**—A solution of this is practically a bacterial vaccine. The bacteria, *Mycobacterium tuberculosis*, are dried, ground, mixed with a suitable base, and made into tablets. The diluent is adjusted so that one tablet dissolved therein will represent the desired amount of new tuberculin B. E. dried, per cc.

**NEW TUBERCULIN-T. R.**—Tuberkelbacillin Rest, Koch.—Tuberculin Residue.—Tuberculin Rückstand.—This is made from living dried tubercle bacilli, *Mycobacterium tuberculosis*, by grinding to complete disintegration. The water insoluble material is suspended in glycerin and water. The final product contains the residue of 10 mg. of dried tubercle bacilli in each cc. of fluid.

New tuberculin is an uncolored, slightly opalescent liquid. It is used occasionally in the treatment of tuberculosis.

**NEW TUBERCULIN T.R.DRIED.**—Tuberculin Residue (Dried).—The mass culture of *Mycobacterium tuberculosis* is repeatedly ground and washed until all water soluble material has been removed. The residue is then ground to complete disintegration, dried, mixed with a suitable base and made into tablets. Each tablet represents a definite amount of dry tubercle bacilli.

**TUBERCULIN DENYS.**—Tuberculine Bouillon Filtré.—Bouillon Filtrate Tuberculin.—This is prepared like old tuberculin, without the prolonged heating and concentration; that is, it is simply a glycerin-broth culture of the tubercle bacillus, *Mycobacterium tuberculosis* passed through a porcelain filter. It contains all the soluble products of the growth of the tubercle bacillus.

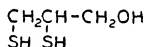
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## CHAPTER XXIII

# Unclassified Therapeutic Agents

This chapter is created as a repository for agents of definite value that cannot logically be described with those classified as having a common therapeutic purpose.

**2,3-DIMERCAPTOPROPANOL IN OIL.**—**Bal in Oil.** H. W. & D.—A solution of 2,3-dimercaptopropanol 10 per cent in peanut oil, containing benzyl benzoate 20 per cent. The structural formula of 2,3-dimercaptopropanol may be represented as follows:



For tests and standards, see Section B.

*Actions and Uses.*—2,3-Dimercaptopropanol in oil is indicated in the treatment of arsenic, gold and mercury poisoning. Results in the treatment of other heavy metal poisoning such as antimony and bismuth have been inconclusive and results in lead poisoning have been disappointing.

2,3-Dimercaptopropanol, by virtue of being a dithiol, competes with physiologically essential cellular -SH groups for arsenic, mercury, and gold, thus preventing combination of the heavy metal with these groups. The stable combination of 2,3-dimercaptopropanol and heavy metal is rapidly excreted and the body thus freed quickly of the toxic agent.

2,3-Dimercaptopropanol is particularly useful in the treatment of hemorrhagic encephalitis due to massive arsenotherapy, arsenical or gold dermatitis, and possibly postarsenical jaundice but not homologous serum jaundice following parenteral therapy. It is useful as an adjunct in the treatment of agranulocytosis due to arsenic but other measures, principally massive doses of penicillin, must also be employed.

While 2,3-dimercaptopropanol in oil is indicated in the treatment of mercury poisoning, it must be remembered that mercury causes rapid and extensive tissue damage, particularly to the kidneys, which cannot be corrected by the administration of 2,3-dimercaptopropanol. The use of 2,3-dimercaptopropanol

in oil in the treatment of mercury poisoning is still in the experimental stage and definite recommendations cannot be made.

The toxicity of 2,3-dimercaptopropanol appears to be less in patients suffering from arsenic, gold, or mercury poisoning, but doses of 300 mg. per Kg. may produce hausea, vomiting and headache, a burning sensation of the lips, mouth, throat and eyes, generalized muscular aches with burning and tingling of the extremities; and a sense of constriction in the chest. The symptoms usually subside in 30 to 90 minutes.

**Dosage.**—In the treatment of arsenic or gold poisoning, 3 mg. per Kg. of 2,3-dimercaptopropanol (as a 10 per cent solution in oil) should be administered by intramuscular injection every four hours for the first two days, four injections on the third day, and injections twice daily thereafter for ten days or until complete recovery. In milder cases, the dose may be reduced to 2.5 mg. per Kg.

HYNSON, WESTCOTT & DUNNING, INC.

**Solution Bal in Oil:** 4½ cc. ampuls. 2,3-Dimercaptopropanol 10 per cent and benzyl benzoate 20 per cent in peanut oil.

### Gold Compounds

The clinical use of gold salts in the treatment of arthritis has been in vogue since 1927, and since 1935 has come to be rather generally recognized as having some value in selected and carefully supervised cases of progressive rheumatoid arthritis unrelieved by older and safer methods of treatment. Its mechanism is not understood. According to the editorial review of Philip S. Hench (*Annals of Internal Medicine*, 6:618, 1947), somewhat over half of the reported patients obtain symptomatic relief, completely in up to a sixth. Up to three-fourths of the improved cases relapse after a time, but may again improve under further treatment. The improvement usually does not begin until the gold injections have been continued for one to three months. This makes it difficult to assign a specific value to the gold treatment, especially as rheumatoid arthritis is potentially reversible without gold. Some skeptical observers consider the results about equal, with or without gold; but more are inclined to conclude that gold plays a positive role, since the successes have generally been scored on patients in whom other measures have failed. The few control series, including a "blindfold" test also note improvement rates of some five to ten times higher with gold than without. However, these chances of usually partial success must be weighed against the risk of very serious toxic reactions in some five per cent of the patients. Minor or moderate transient toxicities develop in nearly half the cases.

For several years the Council has recognized the use of gold salts by injection for the systemic treatment of nondisseminated lupus erythematosus and considers the intramuscular route,

i.e., intragluteal injection, to be the preferred method of administration to obtain the systemic effects of gold compounds. Gold is thus eliminated by the kidneys and at a much slower rate than it is injected, so that a large cumulation remains in the system for as long as a year after treatment is discontinued. On this account and because of the high incidence of reactions (up to 40 or 50 per cent) attributable to the extremely large doses formerly employed in rheumatoid arthritis (100 to 500 mg. for a total of 1.5 to 2 Gm. in a single course of treatment), the Council was previously hesitant to recognize the use of gold salts for the treatment of that disease.

The advent of more conservative dosage for the treatment of rheumatoid arthritis has greatly reduced the rate of reactions, especially the incidence of serious toxic effects. Rather than the enormous dosages formerly employed, experience has shown that therapy should be started with doses of not more than 25 mg. calculated on gold content and continued with gradually increased doses of not more than 50 mg. for women and 75 mg. for men, at weekly intervals, for a total of 500 to 1,000 mg. for a single course of treatment. A total dosage of up to 2,000 mg. is sometimes recommended, but it should be kept in mind that the higher the dosage employed, the greater the chance of reactions—perhaps severe or even fatal in character. Because of this danger, the patient should be examined closely at each visit and a white blood count with differential taken every two or three weeks. The blood sedimentation rate of fall is a good indication of the effects of therapy.

Toxic reactions to gold are of the type seen after other heavy metals, notably arsenicals. The ones mostly to be feared are exfoliative dermatitis, agranulocytosis, purpura and hepatitis. Any skin reaction should demand immediate cessation of further gold therapy and it is doubtful that any patient who has once had a severe reaction should be subjected to further gold therapy. Nitritoid reactions similar to those seen after arsenicals are sometimes encountered. "Gold bronchitis" and polyneuritis have also been observed. Isolated cases of pigmentation have been reported. Patients should be warned of the deleterious effects of exposure to strong sunlight and should not be given actinotherapy as long as the possibility of photosensitization exists.

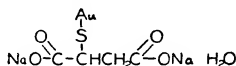
2,3-Dimercaptopropanol (BAL) has been used in the treatment of dermatitis due to aurotherapy. Further discussion of this technic may be found in the BAL monograph.

Gold therapy should not be employed in nephritis, hepatic disease, anemia, hemorrhagic tendency or other blood dyscrasia, tuberculosis or in acute disseminated lupus erythematosus. Patients with the latter disease are peculiarly likely to show an extreme idiosyncrasy for the drug. Gold therapy should not be used in acute rheumatic fever and is of no value in arthritides



other than the active rheumatoid type. It is likewise of little or no value for the chronic stages of rheumatoid arthritis, after the development of extensive deformities has occurred.

**GOLD SODIUM THIOMALATE.**—**Myochrysine-Merck.**—Disodium aurothiomalate.—A gold salt formed by the interaction of sodium thiomalate and a gold halide. It contains about 50 per cent of gold.



For tests and standards, see Section B.

*Actions and Uses.*—Gold sodium thiomalate, like other gold salts, is indicated for the treatment of established cases of active rheumatoid arthritis and for the treatment of nondisseminated lupus erythematosus. Against rheumatoid arthritis it is most effective in relatively early cases, before development of extensive deformities. Gold sodium thiomalate is of no value in the treatment of other arthritides. See also the statement on Gold Compounds.

*Dosage.*—For active rheumatoid arthritis, an initial intramuscular dose of 10 to 15 mg. is suggested in all patients to test tolerance to the drug. Subsequent doses of 25 to 50 mg. at weekly intervals may be given for a total of 700 to 2,000 mg. as a single course. A total amount not to exceed 500 to 1,000 mg. is considered safer. A minimum of two courses is generally given, with an intervening rest period of six to twelve weeks.

For localized lupus erythematosus an initial dose of 5 mg., increased by that amount at weekly intervals to a maximum of 50 mg. for women or 75 mg. for men, is usually recommended.

Toxic reactions are generally minimized by the use of weekly doses not to exceed 25 mg. Transient flushing of the face with giddiness and vertigo may be observed following administration.

MERCK & Co., INC.

**Solution Myochrysine:** 1 cc. ampuls containing 10 mg., 25 mg., 50 mg. or 100 mg. of gold sodium thiomalate, equivalent to 5 mg., 12.5 mg., 25 mg. and 50 mg. of gold, respectively.

U. S. patent 1,994,213 (March 12, 1935; expires 1952) and U. S. trademark 318,390, both assigned to Société des usines Chimiques Rhône-Poulenc, Paris, France.

**GOLD AND SODIUM THIOSULFATE-N. F.**— $\text{AuNa}_3(\text{S}_2\text{O}_3)_2 \cdot 2\text{H}_2\text{O}$ . The complex salt formed from 1 molecule of gold thiosulfate and 3 molecules of sodium thiosulfate. "Contains not less than 36.7 per cent and not more than 37.7 per cent of Au [gold]."—N. F.

For description and standards see The National Formulary under Gold and Sodium Thiosulfate.

**Actions and Uses.**—Gold sodium thiosulfate is used for the treatment of nondisseminated lupus erythematosus and of active rheumatoid arthritis. Its action in these conditions is nonspecific, but has proved beneficial in some cases. It is of no value in chronic forms of arthritis and should not be used in acute rheumatic fever. Also see preceding statement on Gold Compounds.

Even when the doses administered are small, accidents have occurred. The reactions most commonly encountered are varying degrees of fever, diarrhea, vomiting, albuminuria, enteritis, stomatitis, prostration and shock. Skin reactions consist of varying degrees of erythema, urticaria, severe papular and vesicular dermatitis, and scarlatiniform and exfoliative dermatitis. Cases of aplastic anemia, of hemorrhagic diathesis, and of agranulocytosis have also been noted following its use. Published necropsy reports reveal conditions usually found in heavy metal poisoning. A certain number of cases of toxic hepatitis and of acute yellow atrophy have been noted after the use of this drug, likewise isolated cases of generalized pigmentations. Patients to whom gold salts are being administered should be warned of possible deleterious effects from strong sunlight. Moreover, they should not be given actinotherapy.

**Dosage.**—For localized lupus erythematosus the initial dose preferred is 5 mg. intramuscularly given in from 2 to 5 cc. of sterile distilled water. For active rheumatoid arthritis, the initial dose should not exceed 25 mg., the maximum dose should be kept within the same limits, and the total dosage should not exceed 500 to 1000 mg. for one course. Subsequent doses given at weekly intervals are increased 5 mg. per dose, not exceeding a maximum of 50 mg. for women and 75 mg. for men, provided no reactions have occurred. The drug may be continued cautiously in smaller dosage following complete recovery from mild reactions but should be discontinued permanently if severe reactions have occurred.

#### ABBOTT LABORATORIES

**Solution Gold Sodium Thiosulfate:** 10 mg., 25 mg., 50 mg., 75 mg., 0.1 Gm. ampuls.

#### MERCK & Co., INC.

**Solution Gold Sodium Thiosulfate:** 10 mg., 25 mg., 50 mg. ampuls and 75 mg. and 100 mg. bottles.

#### G. D. SEARLE & Co.

**Solution Gold Sodium Thiosulfate with Sodium Thiosulfate and Benzyl Alcohol 2%:** 5 cc. ampuls containing gold sodium thiosulfate 50 mg., sodium thiosulfate U. S. P. 278 mg., sodium sulfite 88 mg. and benzyl alcohol 2 per cent.

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## CHAPTER XXIV

# Vitamins and Vitamin Preparations

### For Prophylactic and Therapeutic Use

#### Vitamins

The investigations of nutrition that have been initiated since the second decade of the present century have afforded an entirely new outlook upon many disorders, some of which have long been suspected to be of dietary origin. This is due to the scientific demonstration that factors other than proteins, carbohydrates, fats and minerals are essential for the preservation of bodily well-being and physiologic function. These factors are designated at the present time as vitamins.

The absence of any one of the vitamins from a diet which is satisfactory in other respects leads to the development of a typical syndrome which is called a "deficiency disease." These diseases may be as striking in their manifestations as are the direct result of underfeeding (caloric deficiency) or deprivation of essential inorganic elements such as iodine, iron, calcium or phosphorus. A striking illustration of a "deficiency disease" is presented by scurvy. This can be entirely averted or effectively cured by the inclusion of foods which contain Vitamin C (ascorbic acid) in the diet. It has been clearly established by convincing experiments that the prophylactic or remedial agent—the antiscorbutic substance—is a definite chemical entity having the composition  $C_6H_8O_6$ . The vitamin is present in many articles used as food, such as fresh vegetables and fruits, yet entirely lacking in others such as the common cereals and grains. Ascorbic acid is readily destroyed by heat under certain conditions, notably in an alkaline medium and in the presence of oxygen. However, foods can be processed without serious loss of ascorbic acid if precautions are taken to exclude air and if the pH of the food is not unfavorable for the preservation of the vitamin.

The foregoing illustration will suffice to indicate the characteristics of a vitamin—a substance essential for maintenance of normal metabolic functions, not identical with the more familiar nutrients, not synthesized in the human body in normally adequate amounts, and therefore to be furnished by an exogenous supply, sometimes more labile than the foodstuffs proper and hence subject to deterioration, and distributed variously among the edible parts of animals and plants. More than twenty

naturally-occurring compounds having vitamin activity have been isolated and identified. There are now available many commercial preparations in pure synthetic form having the same physiologic properties as the naturally-occurring compounds.

For convenience the designations, vitamins A, B, C and D etc., have arisen. Scurvy, beriberi, rickets, pellagra, and xerophthalmia have been attributed with considerable experimental certainty to the lack of specific vitamins; the protective or curative substances are accordingly sometimes spoken of as the antiscorbutic vitamin (C), the antineuritic vitamin ( $B_1$ ), the antirachitic vitamin (D), the pellagra-preventing vitamin, and the antixerophthalmic vitamin (A), etc. Detailed accounts of the physiology of the vitamins can now be found in the newest textbooks on physiological chemistry and nutrition. The problems raised thereby are the subject of active discussion and extensive investigation so that with respect to many features only tentative conclusions should be announced at this time.

Chemical, physical and microbiologic methods are now in general use for the determination of vitamins in pharmaceutical products, but, biologic assays must be used for vitamin D and for checking other determinations. To facilitate such assays and to make uniform the expression of vitamin content, the World Health Organization of the United Nations has sponsored the preparation and distribution of standards for vitamins A,  $B_1$ , C and D. The International unit for each of these vitamins is defined in terms of the biological activity of a specific quantity of the respective standard. The U. S. P. units for vitamins A,  $B_1$ , C and D are identical in value with the International units. The United States Pharmacopoeial Convention also distributes prototype standards for these four vitamins, and in addition reference standards for riboflavin and nicotinic acid.

The Council has decided that when practicable, vitamin content should be stated in milligrams in preference to micrograms or units. This action was prompted by recognition that confusing practices have grown up in the industry concerning representations for the vitamin content of products. The vitamin content of some products has therefore been expressed in micrograms even though the term is wholly unfamiliar to the laity. As a result of this the purchaser may be led to believe that a product has a higher vitamin content when so represented than if units or milligrams were used. For instance one milligram of vitamin  $B_1$  equals 333 U. S. P. or International Units, or 1,000 micrograms. A very similar situation prevails with respect to riboflavin. The decision is applicable to ascorbic acid, thiamine, riboflavin, nicotinic acid, and vitamin K preparations, and will be applied to other vitamins for which no units have been established. Vitamin A and vitamin D content should be expressed in U. S. P. units.

In recent years considerable information has been acquired relating to human requirements for vitamins. It is now possible to specify within rather narrow limits quantities that will suf-

fice to protect against deficiency. Ordinarily there is no reason why a properly selected diet should not afford an adequate supply of the requisite vitamins. Furthermore, with the exception of pellagra, there is no evidence of any noteworthy prevalence in this country of conditions in adults that might properly be ascribed to a severe deficiency of one or more vitamins. However, it must be admitted that under circumstances bringing about a highly restricted dietary regimen and leading to "one-sided" diets a relative shortage of some of the vitamins does at times arise. In almost all such instances the situation can be properly corrected by prescription of appropriate foods. Occasionally, and particularly with infants, a corrective result may be more effectively secured by the administration of products especially rich in the desired vitamin; for example, cod liver oil as a dietary adjunct in the prevention or treatment of rickets, and orange juice in the relief of scurvy.

The clear indications for such specific vitamin therapy are still few in number. The chief justification for the recognition of special vitamin-bearing products at present applies to unusual concentrations of the desired potent principle that they may represent or to exceptionally desirable dosage forms. Multivitamin preparations, particularly capsules, have come into very extensive use in recent years. In most of these preparations the proportion of vitamins present has borne no relationship to established therapeutic dosages, nor to normal requirements for the vitamins. For various reasons the Council has opposed the use of such preparations. The Council will consider for acceptance multivitamin preparations in which the vitamin content is in proportion to the daily needs for the vitamins. This subject is discussed in a report published in the *Journal* (119: 948, July 18, 1942).

## GENERAL PROVISIONS AND LABELING REQUIREMENTS

*Statement of Vitamin Potency.*—When vitamin A or vitamin D potency is expressed, it must be in U. S. P. units. When the vitamin content of preparations of ascorbic acid, thiamine, riboflavin, nicotinic acid, nicotinamide, pyridoxine, menadione and similar vitamin K preparations is expressed, it must be in milligrams and not in micrograms, gammas, or units.

Vitamin preparations which supply in the recommended daily intake not more than three times the minimum daily requirements set forth in regulations under Section 403 (j) of the Food, Drug and Cosmetic Act, must be labeled to show the proportion of the minimum daily requirements supplied in the recommended daily intake.

Vitamin preparations which supply in each unit (tablet, capsule, etc.) or in the recommended daily intake more than three times the minimum daily requirements set forth in regulations under Section 403 (j) of the Food, Drug and Cosmetic Act will be accepted if they are advertised only to the physician. To meet the requirements of the Food, Drug and Cosmetic Act

with respect to adequate directions for use, such preparations must bear the statement ". . . daily, or as prescribed by the physician. This dosage is in excess of the quantity needed for prevention of . . . deficiency," or a more detailed statement of directions for use.

The above labeling requirements are exemplified in the following outline of statements which should appear on the main panel of the label:

#### STATEMENTS REQUIRED ON MAIN LABEL

##### *For Preparations Supplying More Than Three Times the Minimum Daily Requirements*

Quantity of contents:	50 tablets
Common or usual name:	Thiamine Hydrochloride Tablets
Quantity of vitamin in tablets consumed daily:	10 milligrams
Adequate directions for use:	Dose: One tablet daily, or as prescribed by the physician. This dosage is in excess of the quantity needed for prevention of thiamine deficiency.
Name and place of business:	John Doe 550 Broad Street Chicago, Illinois

##### *For Preparations Supplying Three Times the Minimum Daily Requirements or Less*

Quantity of contents:	100 tablets
Common or usual name:	Thiamine Hydrochloride Tablets
Quantity of vitamin in tablets consumed daily:	1 milligram
Dose: This is optional	
Proportion of minimum daily requirement:	1 tablet will supply the minimum daily requirement for an adult.
Name and place of business:	John Doe 550 Broad Street Chicago, Illinois

### General Allowable Claims for Vitamins

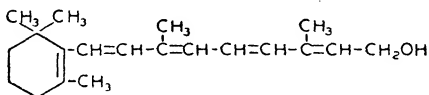
*Growth.*—A deficiency of any food essential will undoubtedly lead to retardation of growth. This is true of each of the essential vitamins but it is equally true of each of the essential amino acids, minerals, and of energy-yielding compounds. Statements conveying the impression that one vitamin is more important than other vitamin or food essential in promoting growth are therefore considered misleading and objectionable.

**Infections.**—A person suffering from malnutrition is more susceptible to certain types of infections than the normal individual. The types of infections which may occur in malnutrition have not been shown to be more closely correlated to specific deficiencies than to the organisms to which the body may be exposed. Secondary infections are characteristic of conditions resulting from severe vitamin deficiency. Investigations have failed to show that the administration of vitamins far in excess of bodily needs makes one more resistant to disease than the ingestion of quantities which are just sufficient to meet normal metabolic requirements.

## Vitamin A

The term "vitamin A" has been applied to any one of several substances or to a mixture of them producing a certain demonstrable specific physiological effect. It seems to have been definitely established that there are at least five substances which can produce to some degree this characteristic response in the animal body. These are vitamin A itself, alpha, beta and gamma carotene and cryptoxanthin. The last four of these, the precursors of vitamin A, are produced in the plant kingdom, and ingestion of these substances by most animals results in varying degree (depending on the species of animal and the precursor fed) in the formation of a compound having the empiric formula  $C_{20}H_{29}OH$  and to which no other name than vitamin A has been given. The extent to which the different precursors of vitamin A can be converted to vitamin A by different species of animals has not definitely been established. The exact function of vitamin A has not been established, but the pathologic picture which results from varying degrees of deficiency has been the subject of extensive investigation.

Vitamin A has the following structural formula:



The claims recognized for vitamin A shall be recognized for the precursors of vitamin A only under conditions specified for Carotene.

Acceptance of Vitamin A preparations will be limited to those containing in each capsule, tablet or average dose of fluid, 25,000 U. S. P. units, or less, of Vitamin A.

**Allowable Claims.**—1. Evidence for the existence of vitamin A and its role in human nutrition is based on the fact that a characteristic eye disease, usually called xerophthalmia, results from a deficiency of this vitamin.

2. It is generally agreed that the first symptom or at least one of the first clinical symptoms of vitamin A deficiency is night-blindness, or nyctalopia. For this type of night blindness

vitamin A is a specific. Cases of nyctalopia exist which do not respond to treatment with vitamin A. These may be due to congenital defects or to other diseases than avitaminosis "A." In view of present knowledge, the claim is not acceptable that the administration of vitamin A to drivers of automobiles will diminish the chance of accident from driving at night.

3. Vitamin A is reported to be effective in the treatment of certain types of hyperkeratosis of the skin of persons suffering from severe deficiency of vitamin A.

4. Vitamin A in excess of normal requirements has not been shown to be of value in the prevention of colds, influenza and such infections.

5. There is at the present time inadequate evidence to warrant the claim that the ingestion of sufficient vitamin A will prevent the formation of renal calculi in man or that it is useful in the treatment of hyperthyroidism, anemia, degenerative conditions of the nervous system, sunburn, or ulcerative conditions of the skin.

### The Vitamin B Complex

The term Vitamin B Complex is applied to a group of substances which have been shown to be constituents of what was formerly called vitamin B. Intensive investigations have produced an ever changing picture of the constituents which comprise the complex. At this writing eight compounds recognized as members of the vitamin B complex have been identified and are being manufactured by synthetic processes. They are:

Thiamine (vitamin B<sub>1</sub>) or Thiamine Hydrochloride (vitamin B<sub>1</sub> hydrochloride), the antiberiberi vitamin which prevents beriberi in man and polyneuritis in animals. See section on Thiamine, for further discussion.

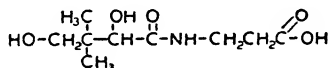
Riboflavin, a component of an oxidation-reduction system of living cells. The only name suggested for the syndrome following a deficiency of this vitamin is ariboflavinosis. See following section on Riboflavin for further discussion.

Nicotinic Acid (amide), (P-P factor), a nutritional factor effective in the treatment of human pellagra. See following section on Nicotinic Acid and Nicotinic Acid Amide for further discussion.

Pyridoxine (Vitamin B<sub>6</sub>) or Pyridoxine Hydrochloride (vitamin B<sub>6</sub> hydrochloride), a factor for the prevention of nutritional dermatosis in rats. There is yet no satisfactory evidence relating to its therapeutic value for man.

Pantothenic Acid, a factor for the prevention of nutritional dermatosis in chicks and necessary for the growth of rats. Its value in human nutrition has not been demonstrated.

Pantothenic acid has the following structural formula:







are conditions which probably could be designated as "latent beriberi"; it does not seem wise at this time to attempt the formulation of a definite statement covering such conditions other than that presented in Item 5.

2. Thiamine may be cited as of value in correcting and preventing anorexia of dietary origin in certain cases.

There are many causes of anorexia, some referable to infections and the reactions thereto, others to organic disorders, and still others related to faulty diet. Where there is no rather obvious cause of anorexia in question, other than a possible dietary one, it is permissible to claim that thiamine may be of therapeutic value when the condition to be treated is due to a deficiency of that vitamin.

3. The administration of thiamine in excess of that present in the ordinary diet may be advantageous when there are specific conditions indicating interference with proper assimilation of the vitamins.

The present status of research on the clinical use of thiamine for specific diseases other than beriberi and for infant feeding, is such that *definite* claims for therapeutic value in relation to such diseases cannot be recognized. Its use may be indicated, however, in such restricted conditions as pernicious vomiting of pregnancy, tube feedings through a jejunal fistula, and the like, because the above permitted statement applies to such conditions and gives an intelligent basis for such therapy.

4. While it has not been established that thiamine deficiency is the sole cause of conditions described as alcoholic neuritis, the neuritis of pregnancy and the neuritis of pellagra, there is some definite evidence of the value of this vitamin in the treatment of these conditions. Vague representations with respect to the value of thiamine in the treatment of other types of neuritis are not permissible.

5. Thiamine deficiency in animals is associated with dysfunctions of the heart and of the vascular system. Thiamine is effective in reestablishing the normal function of the cardiovascular system if the dysfunction was caused by thiamine deficiency. Evidence is lacking that thiamine is effective in any other type of heart disease. At times organic heart disease and beriberi heart coexist. Administration of thiamine is justified in these patients.

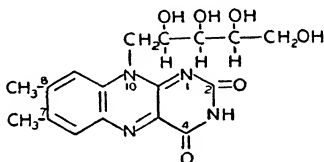
6. It appears that there is an increased requirement for thiamine when there is greatly augmented metabolism such as occurs in febrile conditions, hyperthyroidism, or vigorous muscular activity.

7. Claims for concentrates containing thiamine offered for clinical use should state the potency of this agent in terms of milligrams. The term "concentrate" or a synonym will not be recognized if the product does not exceed a potency of 0.075 mg. per gram (or per cubic centimeter), or if it is a natural product which may have been subjected to a process of dehydration.

## Riboflavin

Riboflavin, the empirical formula of which is  $C_{17}H_{20}N_4O_6$ , was formerly known as Vitamin G, Vitamin B<sub>2</sub>, or Lactoflavin. The chemical nature of the vitamin was established in 1935. In 1936 the Council voted to accept riboflavin for purposes of standardization and clinical experimentation. Since that time sufficient evidence has been accumulated to justify the acceptance of the product as a therapeutic agent. The vitamin is equally effective whether administered orally or parenterally.

Riboflavin has the following structural formula:



*Allowable Claims.*—1. Riboflavin is recognized as a specific in the treatment of certain characteristic lesions of the tongue, the lips, and the face. The symptoms may be described briefly as follows: A typical glossitis may often be observed before other signs of riboflavin deficiency are present. In contrast to the glossitis of pellagra, the tongue is clean, the papillae are flattened or mushroom-shaped rather than atrophic, and the color is definitely purplish-red or magenta instead of being scarlet as in nicotinic acid deficiency. As the disease progresses, the lips become reddened, then shiny and denuded, with maceration and fissuring of the angles of the mouth (cheilosis). Frequently, seborrheic follicular keratoses occur at the nasolabial folds and even over the nose and forehead. The above symptoms are promptly alleviated by the administration of adequate amounts of riboflavin.

2. Riboflavin deficiency is responsible for certain ocular manifestations characterized by itching, burning and a sensation of roughness of the eyes (keratitis), accompanied by mild photophobia. The anatomical changes may vary from a superficial invasion of the cornea by capillaries to an extensive vascular proliferation, with or without infiltration, opacity, and exudate formation. These symptoms, when due to a riboflavin deficiency, are relieved promptly by the administration of the vitamin.

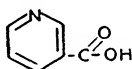
3. It is permissible to recommend the use of riboflavin for the alleviation of symptoms of riboflavin deficiency encountered in other diseases, notably pellagra.

## Nicotinic Acid and Nicotinamide

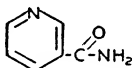
Nicotinic acid ( $C_6H_5ON_2$ ) and nicotinamide ( $C_6H_6ON_2$ ) are of fundamental importance in the treatment of pellagra. The terms, niacin and niacin amide, are now officially recognized

as synonyms for these chemical names. The pure compounds have been known for many years, but not until recently were they recognized as therapeutic agents. In 1938 the Council voted to accept nicotinic acid and nicotinamide "for purposes of standardization and clinical experimentation." Sufficient evidence has now been accumulated to demonstrate the usefulness of these drugs. Administration of relatively large doses of nicotinic acid produces a marked flushing of the face and neck sometimes associated with an unpleasant sensation, but the reaction is transient and apparently harmless. The effect is not observed following the administration of nicotinamide. For parenteral use nicotinamide is the drug of choice.

Nicotinic acid has the following structural formula:



Nicotinamide has the following structural formula:

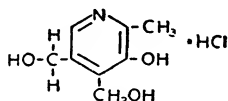


*Allowable Claims.*—1. Nicotinic acid and nicotinamide are recognized as specifics only in the treatment of pellagra. Their administration in appropriate doses lead to the disappearance of all alimentary, dermal, and other lesions, characteristic of the disease, to a return to normal of the porphyrin and porphyrin-like pigments of the urine, and to a profound improvement in the mental symptoms when the latter are the result of an inadequate intake of nicotinic acid and nicotinamide. These compounds are without influence upon the polyneuritis or cheilosis so frequently observed in pellagrous patients. In such cases it may be necessary to insure the presence in the diet of foods rich in vitamin B<sub>1</sub> or B<sub>2</sub>, or to administer thiamine hydrochloride, riboflavin or both.

## Pyridoxine

The terms "pyridoxine" and "pyridoxine hydrochloride" are synonymous with "vitamin B<sub>6</sub>" and "vitamin B<sub>6</sub> hydrochloride."

Pyridoxine hydrochloride has the following structural formula:

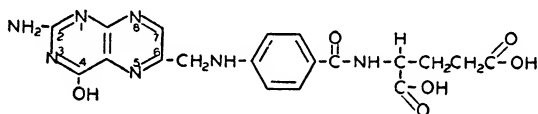


Carefully controlled studies have failed to demonstrate conclusively the value of pyridoxine in the treatment of human dis-

ease, or that there is pyridoxine deficiency in our diets. Further study of the clinical value of this compound is necessary before definite claims will be permitted. Pyridoxine is accepted to assure the availability of a preparation of satisfactory composition for investigational use.

### Folic Acid

Folic acid has been referred to as "Vitamin M," "L. casei Factor," "Vitamin Bc" and "Folic Acid." The chemical name of the synthetic compound has been abbreviated to Pteroyl glutamic acid. The structural formula for the synthetic compound is:



Folic acid produces a response when used in the treatment of pernicious anemia and some other macrocytic anemias in man, and in experimental macrocytic anemias due to dietary deficiencies in monkeys, growing chicks and in fish.

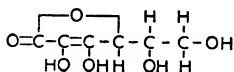
Only a small portion of the folic acid found in many foods occurs in the free form and it is not yet clear to what extent the combined forms can be utilized by man. The combined forms differ chemically from free folic acid in that they contain additional molecules of glutamic acid and they may be rendered active after hydrolysis with suitable enzymes or acids. It is of great interest that highly purified liver extracts effective in macrocytic anemias contain only traces of folic acid, too small to be effective clinically. The relationship between liver extract and folic acid is not yet clear.

### Ascorbic Acid

(Cevitamic Acid)

Suboptimal intakes of ascorbic acid result in the development of clinical and pathologic phenomena to which the descriptive term scurvy has been applied.

Ascorbic acid has the following structural formula:



All pure ascorbic acid that has been used in pharmaceutical products in recent years has been prepared synthetically. The International unit for ascorbic acid, which was formerly defined

as the vitamin C activity of 0.1 cc. of lemon juice, is now defined as the activity of 0.05 mg. of ascorbic acid. This is the quantity of ascorbic acid usually found in 0.1 cc. of lemon juice or orange juice.

In planning diets for infants who do not receive breast milk, and for small children, it is generally advisable to make special provision for a source of ascorbic acid such as orange juice because (a) the concentration of ascorbic acid in fresh cow's milk is only about one-fourth of the concentration in mother's milk, and (b) the vitamin in most foods is very sensitive to destruction by oxidation.

*Allowable Claims.*—1. Ascorbic acid is acceptable for the correction and prevention of scurvy. Definite claims for the therapeutic value of ascorbic acid should be permitted only in relation to scurvy until further clinical or experimental evidence has substantiated its usefulness in other states.

2. It may be permissible under certain conditions to refer to the therapeutic value of ascorbic acid in early and latent scurvy. Convincing clinical evidence has established that this state does occur. It would be well to emphasize the fact that the diagnosis rests, however, on the basis of roentgenologic evidences in the long bones, the blood level, and possibly failure to excrete an optimum amount of ascorbic acid in the urine.

3. Dental caries, pyorrhea, certain gum infections, anorexia, anemia, undernutrition and infection alone are not in themselves sufficient indications of ascorbic acid deficiency but according to experimental and clinical investigation may be concomitant signs of ascorbic acid deficiency. Therefore, it is permissible to accept the claim for the therapeutic value of ascorbic acid in these symptomatic conditions *only when* it is definitely stated that they are the consequences of a deficiency or suboptimal amount of ascorbic acid or when there is a pathologic interference with assimilation of the amount necessary for the preservation of health.

4. Because ascorbic acid is a dietary essential its administration in concentrated form is of value in conditions where difficulty is encountered in introducing it orally or in utilizing ordinary foods in the usual way. Ascorbic acid is accepted as an essential dietary constituent in infant feeding but it should not be accepted for use in the treatment of diseases except according to the conditions mentioned above. It is generally administered in the form of an ascorbic acid carrying juice. It may be administered parenterally in concentrated form as sodium ascorbate when persistent vomiting, diarrhea, or other conditions prevent the utilization of proper amounts taken orally.

5. Dosage forms of ascorbic acid offered for clinical use must state the potency in terms of milligrams.

6. A reasonable general statement regarding allowable claims for ascorbic acid would be as follows:

An optimum amount of ascorbic acid should be supplied at all ages for its therapeutic value in preventing the development of acute or latent scurvy.

Claims for the therapeutic value of ascorbic acid may be accepted when the agent is described as a corrective measure for scurvy due to a demonstrable absence or a suboptimal quantity in the diet, or in cases in which it is definitely known that there is interference with the absorption of an optimal amount.

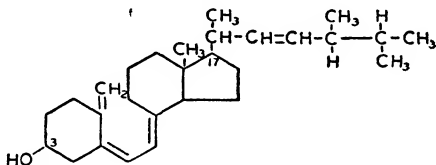
Advertising of ascorbic acid for such symptoms as failure to gain in weight or stoppage of growth, anorexia, anemia, infections, symptoms referable to the central nervous system or hemorrhagic conditions cannot be accepted unless it is definitely stated that the symptoms are referable to a demonstrable deficiency of ascorbic acid.

Ascorbic acid is easily decomposed in the presence of certain other substances; therefore, care should be exercised against administering it (or orange juice) in mixtures, or by any procedure which renders it ineffective.

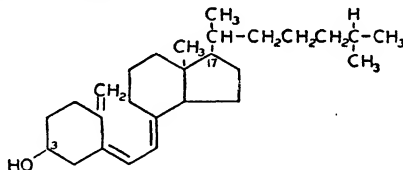
### Vitamin D

The term "vitamin D" is applied to two or more substances which have a function in the proper utilization of calcium and phosphorus. Two forms of naturally occurring vitamin D have been isolated. One of these, vitamin D<sub>2</sub>, or calciferol, is obtained in pure crystalline form as one of the products of the ultra-violet irradiation of ergosterol, the other, vitamin D<sub>3</sub>, can be prepared in the same manner from 7-dehydro-cholesterol. Antirachitic activation of these compounds can also be accomplished by electronic bombardment. The two forms of vitamin D, as well as some of the other products of irradiated ergosterol, possess antirachitic potency. They also tend to elevate the level of serum calcium, an effect which varies, however, with the different substances and which does not parallel the antirachitic effect.

Vitamin D<sub>2</sub> has the following structural formula:



Activated 7-dehydro-cholesterol (vitamin D<sub>3</sub>) has the following structural formula:



Some reports have appeared claiming clinical improvement in chronic arthritis and in certain allergic disorders as a result of the use of massive doses of vitamin D. Critical examination of these reports reveals little to warrant the belief that the clinical effects claimed are specific. There is suggestive clinical evidence that the use of massive doses of vitamin D may cause improvement in some cases of psoriasis, but the effect is not yet well enough established to justify a claim for such use. The Council believes that further studies should be conducted, but, because of the possible toxic effects of large doses of vitamin D, it is necessary that such studies should be made only in clinics where close supervision is possible. The Council also holds there is not sufficient evidence to warrant the acceptance of viosterol preparations of high potency for use in the treatment of arthritis.

Another suggested use of massive doses of vitamin D is in the treatment of refractory rickets, that is, occasional cases of rickets which do not respond to treatment with the usual dosages or even much larger dosages of vitamin D. In some of these cases the rickets is due to a disturbance of the acid base balance and has been successfully treated by administration of sodium bicarbonate or a sodium citrate-citric acid mixture. Massive doses of vitamin D have proved effective in the control in others. The quantity of vitamin D needed may be so large that it borders on the dosages of vitamin D that are definitely toxic, and such treatment should not be undertaken without first exploring other possibilities or without careful observation for signs of toxicity. Some investigators believe it desirable to examine the urine daily for calcium casts, albumin and red blood cells while the maintenance dose is being established. Others believe less frequent examination is necessary. After the dose is established weekly examination, using the Sulkowitch test for excessive excretion of calcium, is sufficient. The blood should be examined weekly or oftener to avoid a rise of calcium above 12 mg. per hundred cubic centimeters if the dosage exceeds 20,000 units daily for the infant or 50,000 units for a child. If anorexia or nausea should appear, the child must be brought promptly to the attention of the physician and vitamin D administration should be discontinued. When the maintenance dose has been established, operative procedures to correct rachitic deformities may precipitate a temporary state of toxicity and the blood levels of calcium must be watched closely.

It is now well established that certain substances derived from activation products of ergosterol and cholesterol are effective in raising the level of serum calcium. This result is achieved in part by mobilization of calcium from the bones but also by an increased absorption of calcium; only Vitamin D<sub>2</sub> (calciferol) and dihydrotachysterol have received extensive clinical trials. Either of these substances may be administered by mouth over considerable periods of time and with reasonable safety provided the serum calcium is not permitted to rise above normal levels. There appears to be no development of tolerance.

Vitamin D<sub>2</sub> (calciferol) and dihydrotachysterol have similar



effects in comparable doses, and it has not been shown that one is superior to the other in the management of hypoparathyroidism. During their use frequent determinations of serum calcium are desirable; the Sulkowitch test, by which the excretion of calcium into the urine is observed is helpful and is so simple that it may be performed by the patient. Its routine use during treatment will reduce the number of necessary determinations of serum calcium.

Treatment of parathyroid insufficiency is commonly initiated with relatively large doses of the activated sterols, followed by smaller maintenance doses. The management of acute parathyroid tetany may require from 2 to 8 mg. of pure dihydrotachysterol which is approximately equivalent to 10 to 40 mg. or 400,000 to 1,600,000 international units of vitamin D. The amount of the substances necessary for daily maintenance varies greatly in individual cases but averages between 0.6 and 1.0 mg. of pure dihydrotachysterol or 3.0 to 5.0 mg. (133,333 to 200,000 international units) of vitamin D.

*Allowable Claims.*—1. Vitamin D is recognized as a specific in the treatment of infantile rickets, spasmophilia (infantile tetany) and osteomalacia, diseases which are manifestations of abnormal calcium and phosphorus metabolism. Vitamin D is valuable in the prevention as well as in the curative treatment of these diseases. Complications such as renal insufficiency or glandular malfunction may preclude normal response to vitamin D therapy. During acute infections, especially of the gastrointestinal tract, vitamin D may prove ineffective because poorly absorbed.

2. Direct exposure of the skin to ultraviolet rays from the sun or from artificial sources results in the formation of vitamin D within the organism but the Council cannot recognize statements or implications that vitamin D has all beneficial effects of exposure to sunshine.

3. There is clinical evidence to justify the statement that vitamin D plays an important role in tooth formation. Likewise experimental evidence justifies the statement that vitamin D is a beneficial factor in preventing and arresting dental caries when the intake of calcium and phosphorus is liberal and the diet is adequate with respect to other nutrients. Claims should not state or imply that vitamin D is the only important factor in caries prevention or arrest.

4. Animal experimentation has shown that correction of an inadequate intake of vitamin D results in the more economical utilization of calcium and phosphorus and also that the undesirable effects of improper ratios of calcium and phosphorus in the diet can largely be overcome by normal intake of vitamin D. The importance of these observations in their application to man is not entirely apparent because of the lack of adequate clinical evidence showing the availability of different forms of calcium and phosphorus, but it may be stated that vitamin D has a favorable influence on calcium and phosphorus metabolism.

5. Because of its effect upon the level of serum calcium, vitamin D has been used in correcting the hypocalcemia of parathyroid tetany. Satisfactory effects may be obtained with sufficient doses either of vitamin D<sub>2</sub> (calciferol) or of dihydrotachysterol, a derivative of one of the products resulting from the irradiation of ergosterol. When vitamin D preparations are employed for the correction of hypocalcemia, patients must be under constant observation since the elevation of serum calcium above normal levels may be accompanied by serious or even fatal effects.

6. Clinical evidence does not warrant the claim that massive doses of vitamin D are of benefit in chronic arthritis, in allergic disorders, or in psoriasis. If representations are made for use of massive doses of vitamin D in the treatment of refractory rickets they must be accompanied by adequate precautions with respect to the danger of toxic effects and how they can be avoided as indicated in the paragraph immediately preceding the allowable claims for vitamin D.

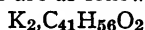
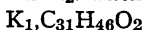
### Vitamin E

In 1925 it was demonstrated conclusively that vitamin E must be included in the diet of the rat to insure successful reproduction. There are at least three naturally-occurring compounds which have vitamin E activity: alpha, beta and gamma tocopherol. There have been comparatively few clinical studies dealing with the role of vitamin E in human physiology and they have not led to very definite conclusions. There seems to be agreement that the vitamin is of no value in the treatment of sterility. There are indications that it may be of value in the treatment of habitual abortion but further studies are necessary to clarify the picture.

Recently there has been renewed interest with respect to vitamin E owing to reports that administration of alpha tocopherol and other preparations of vitamin E have produced beneficial results in the treatment of some cases of degenerative diseases such as amyotrophic lateral sclerosis. This is not substantiated in any way by recent clinical evidence.

### Vitamin K

Vitamin K was discovered and named by Dam of Copenhagen in 1935 when he observed in newly hatched chicks a fatal hemorrhagic diathesis which could be cured or prevented by the administration of a nonsaponifiable nonsterol fraction of hog liver or alfalfa. Later it was observed that the delayed clotting time of the blood was due to low prothrombin content. Investigations have shown that there are at least two naturally-occurring substances having a naphthoquinone nucleus which have similar physiologic properties and they are referred to as vitamin K<sub>1</sub> and vitamin K<sub>2</sub>. Their empirical formulas are as follows:





by the naphthoquinones with analogous activity. The difficulty seems to lie in the fact that the liver cannot utilize the material in the formation of prothrombin, except to a limited degree.

4. The hemorrhagic states, which exist in connection with certain intestinal diseases such as ulcerative colitis, sprue and celiac disease, characterized by either a loss of continuity of the intestinal tract or by a disturbance of its absorptive surface, are also affected in a specific manner by vitamin K.

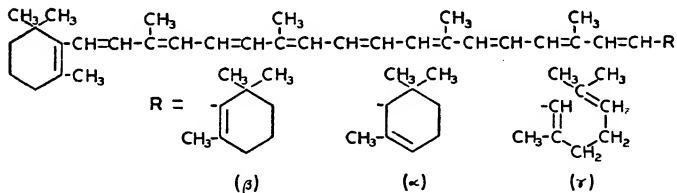
5. In the treatment of the physiological hypoprothrombinemia of the newborn, which exists during the first week of life, the vitamin and its analogues seem to be specific. It seems now fairly well established that the vitamin itself or the naphthoquinones, when administered parenterally to a woman during labor, in amounts as small as  $\frac{1}{2}$  to 2 mg., insures that the newborn infant will have a normal amount of prothrombin in the circulating blood. These doses can also be given parenterally to the newborn infant and will produce the same effect.

## VITAMIN PREPARATIONS

### Vitamin A Preparations

Vitamin A is found in fish liver oils. The provitamin A, carotene, gives the effects of vitamin A when ingested.

**CAROTENE.**—Pro-Vitamin A.—A hydrocarbon having the empiric formula  $C_{40}H_{56}$  which occurs in three isomeric forms referred to respectively as alpha, beta and gamma carotene. The structural formulas of these compounds may be represented as follows:



The alpha form is optically active and the others are not. The beta form appears to predominate in nature, and the gamma is found in the smallest quantities, but usually a mixture of the different forms occurs. The crystals are readily oxidized. They should be kept in a vacuum or in an inert gas in the dark at a low temperature. The International unit for vitamin A adopted at the Second International Conference on Vitamin Standardization, 1934, is defined as the vitamin A activity of 0.6 microgram of beta carotene. There is considerable scientific evidence indicating that alpha and gamma carotene have one-half the vitamin A activity of beta carotene. The Council has reached the following decision with respect to the use of the term "Pro-vitamin

A" as a synonym for carotene: (1) that the term "A Pro-vitamin A" be regarded as a synonym for alpha, beta or gamma carotene or for cryptoxanthin and that the synonym "Pro-vitamin A" be adopted and used in New and Nonofficial Remedies for any combination of two or more of these, and (2) that when this synonym is used on the label of any accepted product, it appear in brackets after the Council name with a statement of the vitamin A potency of the product.

*Actions and Uses.*—It appears that at least a portion of the carotene ingested is converted in the liver into vitamin A. Carotene therefore has actions similar to those of vitamin A. As carotene may be a mixture of the alpha, beta and gamma forms, its relative efficiency may vary according to the ratio of these components. Evidence is not available on which to base the exact conversion factor of carotene in terms of clinical vitamin A effect. Much depends on the conditions for absorption of pigments. The absorption of carotene and, to a lesser degree, that of vitamin A, is decreased in steatorrhea and diarrhea, both acute and chronic. Liquid petrolatum, being a good solvent for carotene, prevents its absorption, and should not be administered together with preparations of carotene. In view of the fact that cases of carotenemia have arisen from overdosage, the Council warns against the administration of too large doses of carotene. The vitamin potencies stated are on the basis of biological assays and not on physical and chemical measurements establishing the identity and purity of the product.

*Dosage.*—See statement under vitamin A and D Preparations. Carotene is generally administered in the form of carotene dissolved in an oily solution.

#### WYETH, INCORPORATED

**Solution Carotene Concentrate in Oil:** 50 cc. bottle. A solution containing carotene in cottonseed oil. It is biologically assayed to have in each gram a vitamin A potency of not less than 7,500 units, U. S. P. Accompanied by a dropper designed to deliver 25 drops to the cubic centimeter.

**Capsules Carotene Concentrate in Oil:** Each capsule contains an amount of carotene equivalent to 5,000 U. S. P. units of vitamin A.

**OLEOVITAMIN A-U. S. P.**—Natural Vitamin A in Oil. —"Fish liver oil, or fish liver oil diluted with an edible vegetable oil, or a solution of Vitamin A concentrate, from natural (animal) sources in fish liver oil or in an edible vegetable oil. Oleovitamin A contains in each Gm. not less than 50,000 and not more than 65,000 U. S. P. units of Vitamin A, and not more than 1,000 U. S. P. units of Vitamin D." U. S. P.

For description and standards see the U. S. Pharmacopeia under Oleovitamin A and Oleovitamin A Capsules.

*Actions, Uses and Dosage:* See statement under vitamin A and D preparations.

ABBOTT LABORATORIES

**Capsules Oleo Vitamin A:** Each capsule contains 25,000 U. S. P. units of vitamin A derived from natural fish liver oils.

INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY

**Capsules Oleo Vitamin A:** Each capsule contains 25,000 U. S. P. units of vitamin A derived from fish liver oils.

PREMO PHARMACEUTICAL LABORATORIES, INC.

**Capsules Vitamin A:** Each capsule contains 25,000 U. S. P. units of vitamin A derived from natural fish liver oils.

WALKER VITAMIN PRODUCTS, INC.

**Capsules Oleo Vitamin A:** Each capsule contains 25,000 U. S. P. units of vitamin A derived from fish liver oils.

WHITE LABORATORIES, INC.

**Capsules Oleo-Blend Vitamin A:** Each capsule contains 25,000 U. S. P. units of vitamin A derived from fish liver oils.

### Vitamin B Complex Preparations

The Council will consider for acceptance the following types of preparations containing mixtures of the components of the vitamin B complex:

(1) Mixtures of pure thiamine, riboflavin and nicotinic acid providing in the recommended daily intake: 1 milligram thiamine, 1.5 to 2 milligrams riboflavin, 10 milligrams nicotinic acid, or simple multiples thereof.

(2) Dried yeast U. S. P. having the following minimum vitamin content per gram: 0.12 milligram thiamine, 0.04 milligram riboflavin, and 0.250 milligram nicotinic acid.

(3) Dried yeast U. S. P. as described under (2), to which has been added riboflavin and nicotinic acid in such quantities that for each milligram of thiamine contained in the finished product there are present 1.5 to 2 milligrams of riboflavin and 10 milligrams of nicotinic acid.

(4) A concentrate of the vitamin B complex from brewer's yeast as described under (2), and providing in the recommended daily intake: 1 milligram of thiamine (or a simple multiple thereof) and corresponding proportions of other known vitamins of yeast.

(5) A concentrate of the vitamin B complex from liver containing in each gram not less than 0.25 milligram of riboflavin.

(6) A concentrate of the vitamin B complex from brewer's yeast fortified with riboflavin and nicotinic acid and providing in the recommended daily intake: 1 milligram thiamine, 1.5 to 2 milligrams riboflavin, and 10 milligrams nicotinic acid, or simple multiples thereof.

(7) A concentrate of the vitamin B complex from rice polish-

ings fortified with riboflavin and nicotinic acid providing in the recommended daily intake: 1 milligram thiamine, 1.5 to 2 milligrams of riboflavin, and 10 milligrams of nicotinic acid, or simple multiples thereof.

**DRIED YEAST-U. S. P.**—Dry Yeast.—“Dried Yeast consists of the dry cells of any suitable strain of *Saccharomyces cerevisiae* Meyen (Fam. *Saccharomycetaceae*). Dried Yeast may be obtained as a by-product from the brewing of beer which has been made from an extract from cereal grain and hops. The yeast cells are washed free of beer and dried, and may or may not be debittered. These yeasts are commonly known, respectively, as ‘Brewer’s Dried Yeast’ and ‘Debittered Brewer’s Dried Yeast.’ Dried Yeast may also be obtained by growing suitable strains of yeast, using media other than those required for the production of beer, and under appropriate environmental conditions. The yeast thus obtained is commonly known as ‘Primary Dried Yeast.’

“Dried Yeast contains not less than 40 per cent of protein and, in each Gm., the equivalent of not less than 0.12 mg. of thiamine hydrochloride, 0.04 mg. of riboflavin and 0.25 mg. of nicotinic acid.”—U. S. P.

For further description and standards see the U. S. Pharmacopeia under Dried Yeast and Dried Yeast Tablets.

**Actions and Uses.**—Yeast extract containing vitamin B complex is proposed for prophylaxis and treatment of conditions arising from deficiency of the vitamin B complex in the diet.

**Dosage.**—Infants: 2 cc. to 4 cc. of the liquid preparation daily; children: 4 cc. to 12 cc. of the liquid preparation; adults: 12 cc. to 24 cc. of the liquid preparation.

#### ABBOTT LABORATORIES

**Tablets Brewer’s Yeast, 0.4 Gm. (Fortified with Riboflavin and Nicotinic Acid):** Each tablet contains Abbott’s Brewer’s Yeast Powder Fortified with Riboflavin and Nicotinic Acid 0.4 Gm., providing in each tablet vitamin B<sub>1</sub> 0.06 mg., riboflavin 0.12 mg., nicotinic acid 0.6 mg. Average daily dose, as a supplement to the diet, for children 6 to 12 years old, 6 tablets; older children and adults, 9 tablets; therapeutic doses must be determined for each patient.

**Tablets Brewer’s Yeast, 0.5 Gm. (Fortified with Riboflavin and Nicotinic Acid):** Each tablet contains 0.5 Gm. of dried brewer’s yeast (*Saccharomyces cerevisiae*), debittered, fortified with crystalline riboflavin and nicotinic acid to contain in each tablet vitamin B<sub>1</sub>, 0.1 mg., riboflavin 0.2 mg. and nicotinic acid 1 mg. Prophylactic dose for adults 10 tablets daily; therapeutic doses must be determined for each patient.

#### Preparation.—

Abbott’s brewer’s yeast tablets are prepared from a selected strain of *Saccharomyces cerevisiae* especially cultured. The yeast cells are washed and dried, the dry powder containing approximately 5 per cent of moisture, and compressed into tablets.

The vitamin B<sub>1</sub> content of the tablets is determined by comparison with the international standard by the modified Smith rat curative method. The vitamin G content is determined by the Sherman-Bourquin method.

#### H. W. KINNEY AND SONS

**Kinney's Yeast Extract Containing Vitamin B Complex (Liquid):** 125 cc. bottles. Biologically assayed to contain in each 1 cc. the equivalent of not less than 0.075 mg. (25 I. U.) of thiamine hydrochloride and 0.025 mg. (10 Sherman-Bourquin units) of riboflavin. Preserved with glycerin and simple syrup.

##### *Preparation.*—

Kinney's yeast extract containing vitamin B complex is prepared by extracting specially cultured dried brewer's yeast in an aqueous medium under proper conditions of pH control. The extract is concentrated and clarified. It is then preserved in liquid form by the addition of an equal volume of a mixture of equal parts of glycerin and simple syrup.

The thiamine hydrochloride content is determined by comparison with the U. S. P. Thiamine Hydrochloride Reference Standard according to the method given under Thiochrome Assay for Thiamine Hydrochloride, page 705, U. S. P. XIII. The riboflavin content is determined according to method given under Riboflavin Assay, page 685, U. S. P. XIII. The glycerin content is estimated according to the method described in "Methods of Analysis," Association of Official Agricultural Chemists, 5th Edition, 1940, page 386, chapter XXVIII, paragraph 55.

#### MCNEIL LABORATORIES, INC.

**Tablets Brewer's Yeast:** 0.3 Gm. Each tablet contains brewer's yeast 0.32 Gm., providing thiamine hydrochloride 0.167 mg. (55.5 U. S. P. units), riboflavin 0.023 mg. and niacin 0.195 mg.

##### *Preparation.*—

Dried Brewer's Yeast—U. S. P.—Granulated with a mixture of calcium carbonate, starch, sodium chloride, dried malt syrup, saccharin, vanillin, oil of chocolate and tale. The mixture is compressed into tablets.

#### MEAD JOHNSON AND COMPANY

**Brewer's Yeast (Powder):** 28.35 Gm. (11 level teaspoons or 3 level tablespoons). Each gram contains not less than thiamine (vitamin B<sub>1</sub>) 0.18 mg., riboflavin (vitamin G) 0.06 mg. and niacin 0.4 mg., together with other factors of the vitamin B complex commonly occurring in brewer's yeast. Dosage for infants, ½ to 1 level teaspoon in the milk formula. For children 1 to 6, 1 to 2 level teaspoons in milk or tomato juice. For use as a supplement in the treatment of deficiencies of various factors of the vitamin B complex, dosage will depend on the type of specific vitamin therapy employed, the severity of the condition and the individual patient; in general, 2 to 4 level teaspoons daily. For supplementary use with specific vitamin therapy in ariboflavinosis and pellagra, 7 or more level teaspoons daily.

**Tablets Brewer's Yeast:** 0.4 Gm. Each tablet contains 0.4 Gm. dehydrated brewer's yeast supplying thiamine hydrochloride 0.06 mg., riboflavin 0.02 mg. and 0.15 mg. niacin together with



other factors of the vitamin B complex commonly occurring in brewer's yeast. Dosage for children, 6 to 10 tablets daily; for adults, 10 to 12 daily; for pregnancy and lactation, 12 to 20 tablets daily. For use as a supplement in the treatment of deficiencies of various factors of the vitamin B complex, dosage will depend on the type of specific vitamin therapy employed, the severity of the condition and the individual patient; in general, 8 to 20 tablets daily. For supplementary use with specific vitamin therapy in ariboflavinosis and pellagra, 35 or more tablets daily.

*Preparation.*—

Mead's brewer's yeast powder is a dried, nonviable strain of *Saccharomyces cerevisiae*, cultured especially for its vitamin content. It is readily suspended in water, milk, tomato juice or other suitable fluids.

**E. R. SQUIBB & SONS**

**Tablets Brewer's Yeast:** 0.4 Gm. Each tablet contains 0.4 Gm. dehydrated brewer's yeast supplying thiamine hydrochloride 0.06 mg., riboflavin 0.03 mg., and niacin 0.15 mg.

**VITAMIN B COMPLEX SYRUP.**—A syrup prepared from a concentrated extract of dried brewer's yeast and an extract of corn processed with *Clostridium acetobutylicum*, with inverted cane sugar 40 per cent w/v and natural flavoring.

*Actions and Uses.*—Proposed for prophylaxis and treatment of conditions arising from deficiency of the vitamin B complex.

**MARVIN R. THOMPSON, INC.**

**Syrup Vitamin B Complex:** Each 5 cc. contains thiamine hydrochloride 1.5 mg., riboflavin 1.0 mg., pyridoxine hydrochloride 0.5 mg., niacin and niacinamide 7.0 mg., with other vitamin B complex factors as extracted from 10 Gm. of dried brewer's yeast.

**VI-Co PRODUCTS Co.**

**Syrup Vitamin B Complex:** Each 5 cc. contains thiamine hydrochloride 1.5 mg., riboflavin 1.0 mg., pyridoxine hydrochloride 0.5 mg. and nicotinic acid 7.0 mg., with other vitamin B complex factors as extracted from 10 Gm. of dried brewer's yeast.

U. S. patent 2,193,876 (March 19, 1940; expires 1957).

## Thiamine Preparations

**THIAMINE HYDROCHLORIDE-U. S. P.**—Betabion-Merck.—Thiamin chloride.—Vitamin B<sub>1</sub> hydrochloride.—Vitamin B<sub>1</sub>.—"When dried at 100 C for 3 hours, contains not less than 98 per cent of C<sub>12</sub>H<sub>17</sub>ClN<sub>4</sub>OS.HCl." U. S. P.

For description and standards see the U. S. Pharmacopeia under Thiamine Hydrochloride, Thiamine Hydrochloride Injection and Thiamine Hydrochloride Tablets.

Acceptance of tablets thiamine hydrochloride will be limited to  $\frac{1}{2}$ , 1, 3, 5 and 10 mg. of thiamine hydrochloride per tablet, and the acceptance of solutions thiamine hydrochloride for parenteral use will be limited to 1, 5, and 10 mg. thiamine hydrochloride per cc. No dosage form in containers larger than 10 cc. size will be considered for acceptance.

*Actions and Uses.*—See article, Thiamine.

*Dosage.*—The minimum daily requirement of thiamine for an adult appears to be approximately 1 mg., and the optimum intake is said to lie between 1.5 and 2.5 mg. For the child, the optimum intake may be calculated from the caloric requirement, by allowing at least 0.03 milligram for each 100 calories. In the well-balanced diet the thiamine requirement should be obtained from the food.

When pharmaceutical preparations of thiamine hydrochloride are prescribed, the minimum daily prophylactic dosage for the infant should not be less than 0.15 mg. and for the adult should not be less than 1 mg. There appears to be no satisfactory evidence that prophylactic dosages in excess of 0.5 mg. for the infant and 3 mg. for the adult are indicated. Evidence on which to base dosages in the treatment of acute deficiencies is meager. There are indications that doses of the order to 10 to 50 mg. may be advantageous in specific instances. Thiamine is rapidly absorbed from the digestive tract and indications for parenteral administration are very limited. Intravenous administration is neither necessary nor desirable. There is evidence indicating that injections of large dosages of solutions of high potency may cause anaphylactic shock.

#### ABBOTT LABORATORIES

**Tablets Thiamine Hydrochloride:** 1 mg., 3 mg., 5 mg. and 10 mg.

**Solution Thiamine Hydrochloride:** 10 mg. per cc. 10 cc. bottle. Each cc. contains thiamine hydrochloride 10 mg., sodium chloride 5.7 mg. and benzyl alcohol 9 mg. in chemically pure water. This preparation is for parenteral administration.

#### AMERICAN PHARMACEUTICAL CO., INC.

**Tablets Thiamine Hydrochloride:** 1 mg., 5 mg. and 10 mg.

#### GEORGE A. BREON & COMPANY, INC.

**Solution Thiamine Hydrochloride:** 10 mg. per cc. 10 cc. vial. Contains sodium chloride 7.5 mg. per cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Tablets Thiamine Hydrochloride:** 1 mg., 5 mg. and 10 mg.

#### BRISTOL LABORATORIES, INC.

**Solution Thiamine Hydrochloride:** 10 mg. per cc. 1 cc. ampuls and 5 cc. vials. Each cubic centimeter contains 10 mg.

of crystalline vitamin B<sub>1</sub> hydrochloride, 5 mg. of chlorobutanol in double distilled water.

BURROUGHS WELLCOME & Co., INC.

**Tabloid Thiamine Hydrochloride:** 5 mg. and 10 mg.

THE DRUG PRODUCTS Co., INC.

**Pulvoids Thiamine Hydrochloride:** 1 mg., 3 mg.

**Solution Thiamine Hydrochloride:** 10 mg. per cc. 1 cc. ampul hyposols.

**Solution Thiamine Hydrochloride:** 10 mg. per cc. 10 cc. hypsol vials. Preserved with 0.5 per cent of chlorobutanol.

R. E. DWIGHT & COMPANY

**Tablets Thiamine Hydrochloride:** 5 mg. and 10 mg.

ENDO PRODUCTS, INC.

**Solution Thiamine Hydrochloride:** 1 mg. per cc. 1 cc. ampuls. Preserved with 0.5 per cent chlorobutanol.

**Solution Thamine Hydrochloride:** 10 mg. per cc. 1 cc. ampuls and 10 cc. vials. Preserved with 0.5 per cent chlorobutanol.

**Tablets Thiamine Hydrochloride:** 1 mg., 3 mg. and 5 mg.

FLINT, EATON & COMPANY

**Solution Thiamine Hydrochloride:** 10 mg. per cc. 1 cc. ampuls.

**Tablets Thiamine Hydrochloride:** 1 mg., 5 mg. and 10 mg.

THE HARROWER LABORATORY, INC.

**Tablets Thiamine Hydrochloride:** 10 mg.

HORTON & CONVERSE

**Tablets Thiamine Hydrochloride:** 1 mg., 5 mg. and 10 mg.

INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY, INC.

**Tablets Thiamine Hydrochloride:** 1 mg., 3 mg., 5 mg. and 10 mg.

KREMERS-URBAN Co.

**Tablets Thiamine Hydrochloride:** 3 mg. and 10 mg.

McKESSON & ROBBINS, INC.

**Tablets Thiamine Hydrochloride:** 0.5 mg., 1 mg. and 3 mg.

MERCK & Co., INC.

**Betabion (Powder):** 1 Gm. bottle.

U. S. trademark 336,518.

**Thiamine Hydrochloride (Powder).**

THE W. M. S. MERRELL COMPANY

**Tablets Thiamine Hydrochloride:** 1 mg., 3 mg., 5 mg. and 10 mg.

E. S. MILLER LABORATORIES, INC.

**Solution Thiamine Hydrochloride:** 10 mg. per cc. 1 cc. ampuls.

**Tablets Thiamine Hydrochloride:** 5 mg. and 10 mg.

NATIONAL DRUG COMPANY

**Solution Thiamine Hydrochloride:** 1 cc. and 10 cc. ampuls.

**Tablets Thiamine Hydrochloride:** 1 mg.

WILLIAM H. RORER, INC.

**Tablets Thiamine Hydrochloride:** 1 mg. and 5 mg.

SCHIEFFELIN & Co.

**Tablets Thiamine Hydrochloride:** 3 mg., 5 mg. and 10 mg.

CARROLL DUNHAM SMITH PHARMACAL COMPANY

**Solution Thiamine Hydrochloride:** 10 mg. per cc. 1 cc. ampuls. Each cubic centimeter contains thiamine hydrochloride 10 mg. in isotonic solution of sodium chloride, preserved with 0.5 per cent chlorobutanol.

**Tablets Thiamine Hydrochloride:** 1 mg., 5 mg. and 10 mg.

SMITH-DORSEY COMPANY

**Solution Thiamine Hydrochloride:** 10 mg. per cc. 10 cc. vials. Each cubic centimeter contains thiamine hydrochloride in an isotonic solution of sodium chloride. Chlorobutanol 0.5 per cent added as a preservative.

**Tablets Thiamine Hydrochloride:** 1 mg., 5 mg. and 10 mg.

E. R. SQUIBB & SONS

**Tablets Thiamine Hydrochloride:** 5 mg. and 10 mg.

WINTHROP-STEARNs, INC.

**Tablets Thiamine Hydrochloride:** 5 mg. and 10 mg.

U. S. VITAMIN CORPORATION

**Solution Thiamine Hydrochloride:** 10 mg. per cc. 1 cc. ampuls and 5 cc. and 10 cc. vials. Preserved with 0.5 per cent chlorobutanol.

**Tablets Thiamine Hydrochloride:** 1 mg., 3 mg., 5 mg. and 10 mg.

## THE UPJOHN COMPANY

**Solution Thiamine Hydrochloride:** 5 mg. per cc. 1 cc. ampuls. Preserved with 0.5 per cent of chlorobutanol.

**Solution Thiamine Hydrochloride:** 10 mg. per cc. 1 cc. ampuls and 10 cc. vials. Preserved with 0.5 per cent of chlorobutanol.

**Tablets Thiamine Hydrochloride:** 1 mg., 3 mg., 5 mg. and 10 mg.

## THE VALE CHEMICAL CO., INC.

**Tablets Thiamine Hydrochloride:** 1 mg., 3 mg., 5 mg. and 10 mg.

## WALKER VITAMIN PRODUCTS, INC.

**Solution Thiamine Hydrochloride (Oral Use):** 0.3 mg. per drop 15 cc. and 60 cc. bottles.

**Tablets Thiamine Hydrochloride:** 1 mg., 3 mg., 5 mg. and 10 mg.

## WARREN-TEED PRODUCTS COMPANY

**Tablets Thiamine Hydrochloride:** 10 mg.

## WHITE LABORATORIES, INC.

**Tablets Thiamine Hydrochloride:** 5 mg.

## WYETH, INCORPORATED

**Tablets Thiamine Hydrochloride:** 5 mg. and 10 mg.

*Mixed Vitamin B Components*

**TRIASYN B-U. S. P.**—"Triasyn B Capsules and Tablets contain in each capsule or tablet not less than 2 mg. of thiamine hydrochloride, 3 mg. of riboflavin and 20 mg. of nicotinamide."—U. S. P.

For description and standards see the U. S. Pharmacopeia under Triasyn B Capsules and Triasyn B Tablets.

*Actions, Uses and Dosage.*—For prophylaxis and treatment of conditions arising from deficiency of thiamine, riboflavin and nicotinic acid. See articles on the various vitamins concerned.

## PREMO-PHARMACEUTICAL LABORATORIES, INC.

**Capsules Triasyn B:** Each capsule contains 2 mg. of thiamine hydrochloride, 3 mg. of riboflavin and 20 mg. of nicotinic acid amide.

**Tablets Triasyn B:** Each tablet contains 2 mg. of thiamine hydrochloride, 3 mg. of riboflavin and 20 mg. of nicotinic acid amide.

## Riboflavin Preparations

**RIBOFLAVIN-U. S. P.**—Lactoflavin. Vitamin B<sub>2</sub>—Vitamin G.

For description and standards see the U. S. Pharmacopeia under Riboflavin, Riboflavin Injection and Riboflavin Tablets.

Acceptance of tablets riboflavin will be limited to 1, 2, 5 and 10 mg. of riboflavin per tablet and the acceptance of solutions riboflavin for parenteral use will be limited to 0.2 mg. Riboflavin per cc., except that special consideration will be given to solutions of higher concentrations that may be obtained by the use of other reagents.

*Actions and Uses.*—See article, Riboflavin.

*Dosage.*—The optimum intake of riboflavin for an infant appears to be approximately 1 mg. per day, and for an adult approximately 3 mg. per day. The requirement during pregnancy and lactation is higher. When riboflavin is used therapeutically the dosage varies from 2 to 10 mg. per day depending upon the severity of the deficiency. No side effects have been noticed following the administration of relatively large doses.

ABBOTT LABORATORIES

**Capsules Riboflavin: 5 mg.**

**Tablets Riboflavin: 1 mg., 5 mg. and 10 mg.**

AMERICAN PHARMACEUTICAL Co., INC.

**Tablets Riboflavin: 1 mg. and 5 mg.**

GEORGE A. BREON & COMPANY, INC.

**Tablets Riboflavin: 5 mg.**

ENDO PRODUCTS, INC.

**Tablets Riboflavin: 5 mg.**

THE HARROWER LABORATORY, INC.

**Tablets Riboflavin: 5 mg.**

INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY, INC.

**Tablets Riboflavin: 1 mg., 2 mg. and 5 mg.**

MERCK & Co., INC.

**Riboflavin (Powder)**

THE WM. S. MERRELL COMPANY

**Tablets Riboflavin: 5 mg.**

PREMO PHARMACEUTICAL LABORATORIES, INC.

**Tablets Riboflavin: 1 mg., 2 mg., 5 mg. and 10 mg.**

## U. S. VITAMIN CORPORATION

Tablets Riboflavin: 1 mg. and 5 mg.

## THE UPJOHN COMPANY

Tablets Riboflavin: 1 mg. and 5 mg.

## WALKER VITAMIN PRODUCTS, INC.

Tablets Riboflavin: 1 mg., 5 mg. and 10 mg.

## WARREN-TEED PRODUCTS COMPANY

Tablets Riboflavin: 1 mg.

### Nicotinic Acid and Nicotinamide Preparations

**NICOTINIC ACID-U. S. P.**—Niacin.—“When dried for 3 hours over sulfuric acid, contains not less than 99.5 per cent of  $C_6H_5O_2N$ .” U. S. P.

For description and standards see the U. S. Pharmacopeia under Nicotinic Acid and Nicotinic Acid Tablets.

*Actions and Uses.*—See article, Nicotinic Acid and Nicotinamide.

*Dosage.*—The optimum intake of nicotinic acid has not been established with certainty. However, for adults, it seems to be of the order of 15 to 20 mg. per day. The dose for therapeutic purposes varies considerably from person to person depending upon the severity of the deficiency, and possibly upon other as yet unknown factors. The maximum quantity to be recommended is 500 mg. per day, given in 10 doses of 50 mg. each.

Acceptance of nicotinic acid tablets will be limited to 25, 50 and 100 mg. of nicotinic acid per tablet. Solutions of nicotinic acid will not be eligible for acceptance.

## ABBOTT LABORATORIES

Tablets Nicotinic Acid: 50 mg. and 100 mg.

## AMERICAN PHARMACEUTICAL CO., INC.

Nicotinic Acid (*Powder*): 30 Gm., 120 Gm. and 480 Gm. packages.

Tablets Nicotinic Acid: 25 mg., 50 mg. and 100 mg.

## GEORGE A. BREON &amp; COMPANY, INC.

Tablets Nicotinic Acid: 100 mg.

## ENDO PRODUCTS, INC.

Tablets Nicotinic Acid: 50 mg. and 100 mg.

## FLINT, EATON &amp; COMPANY

Tablets Nicotinic Acid: 25 mg.

INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY, INC.

**Tablets Nicotinic Acid:** 25 mg., 50 mg. and 100 mg.

MERCK & CO., INC.

**Niacin (Powder).**

THE WM. S. MERRELL COMPANY

**Tablets Nicotinic Acid:** 50 mg.

NATIONAL DRUG COMPANY

**Tablets Nicotinic Acid:** 50 mg. and 100 mg.

THE NEW YORK QUININE AND CHEMICAL WORKS, INC.

**Nicotinic Acid (Powder)**

PARKE, DAVIS & COMPANY

**Tablets Nicotinic Acid:** 50 mg. and 100 mg.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Tablets Nicotinic Acid:** 50 mg.

SMITH-DORSEY COMPANY

**Tablets Nicotinic Acid:** 50 mg. and 100 mg.

U. S. VITAMIN CORPORATION

**Tablets Niacin:** 25 mg., 50 mg. and 100 mg.

THE UPJOHN COMPANY

**Tablets Nicotinic Acid:** 50 mg. and 100 mg.

WALKER VITAMIN PRODUCTS, INC.

**Tablets Nicotinic Acid:** 25 mg., 50 mg. and 100 mg.

WARREN-TEED PRODUCTS COMPANY

**Tablets Niacin:** 50 mg.

**NICOTINAMIDE-U. S. P.**—Nicotinic Acid Amide.—Niacinamide.—“When dried over sulfuric acid for 4 hours, contains not less than 98.5 per cent of  $C_6H_6N_2O$ .” U. S. P.

For description and standards see the U. S. Pharmacopeia under Nicotinamide, Nicotinamide Injection and Nicotinamide Tablets.

*Actions and Uses.*—See article, Nicotinic Acid and Nicotinamide.

*Dosage.*—Same as for nicotine acid.

Acceptance of nicotinamide tablets will be limited to 25, 50 and 100 mg. nicotinamide per tablet and the acceptance of ampul solutions for parenteral use will be limited to 25, 50 and 100 mg. of nicotinamide per cubic centimeter.



## ABBOTT LABORATORIES

**Solution Nicotinamide:** 100 mg. per 2 cc. 2 cc. ampuls.

**Tablets Nicotinamide:** 50 mg. and 100 mg.

## AMERICAN PHARMACEUTICAL Co., INC.

**Tablets Nicotinamide:** 50 mg. and 100 mg.

## GEORGE A. BREON &amp; COMPANY, INC.

**Solution Nicotinic Acid Amide:** 25 mg. per cc. 2 cc. ampuls.

**Tablets Nicotinamide:** 100 mg.

**Tablets Nicotinic Acid Amide:** 50 mg.

## BREWER &amp; Co., INC.

**Solution Niacinamide:** 100 mg. per cc. 10 cc. vials. Preserved with 0.5 per cent chlorobutanol.

## BURROUGHS WELLCOME &amp; Co., INC.

**Solution Nicotinamide:** 100 mg. per cc. 5 cc. rubber capped vial. Preserved with 0.5 per cent chlorobutanol.

## COLE CHEMICAL COMPANY

**Tablets Niacinamide:** 100 mg.

## THE DRUG PRODUCTS Co., INC.

**Solution Nicotinamide:** 50 mg. per cc. 1 cc. ampuls and 100 cc. vials. Preserved with 0.5 per cent of chlorobutanol.

**Pulvoids Nicotinamide:** 50 mg.

## ENDO PRODUCTS, INC.

**Solution Nicotinamide:** 100 mg. per cc. 5 cc. and 10 cc. multiple dose vials. Preserved with 0.5 per cent chlorobutanol.

## FLINT, EATON &amp; COMPANY

**Solution Nicotinamide:** 50 mg. per cc. 15 cc. rubber capped vial.

**Tablets Nicotinamide:** 50 mg.

## THE HARROWER LABORATORY, INC.

**Tablets Niacinamide:** 50 mg.

## INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY, INC.

**Tablets Nicotinic Acid Amide:** 25 mg., 50 mg. and 100 mg.

## LAKESIDE LABORATORIES, INC.

**Solution Nicotinamide, 10% W/V:** 15 cc. vials. Each cubic centimeter contains 100 mg. of nicotinamide in distilled water with 0.5 per cent chlorobutanol.

MERCK & Co., INC.

**Niacinamide (Powder).**

THE WM. S. MERRELL COMPANY

**Tablets Nicotinamide: 50 mg.**

E. S. MILLER LABORATORIES, INC.

**Solution Niacinamide: 50 mg. per cc. 15 cc. vials.** Preserved with 0.5 per cent chlorobutanol.

U. S. VITAMIN CORPORATION

**Solution Niocinamide: 50 mg. per cc. 2 cc. ampuls.**

**Tablets Niacinamide: 100 mg.**

THE UPJOHN COMPANY

**Solution Nicotinic Acid Amide: 100 mg. per cc. 2 cc. ampuls and 10 cc. vials.** Preserved with chlorobutanol 5 mg.

**Tablets Nicotinic Acid Amide: 50 mg. and 100 mg.**

THE VALE CHEMICAL Co., INC.

**Tablets Nicotinamide: 50 mg.**

WALKER VITAMIN PRODUCTS, INC.

**Tablets Niacinamide: 25 mg., 50 mg. and 100 mg.**

WARREN-TEED PRODUCTS COMPANY

**Tablets Nicotinamide: 50 mg.**

## Pyridoxine Preparations

**PYRIDOXINE HYDROCHLORIDE.**—Hexabione Hydrochloride—Merck. — 2-Methyl-3-hydroxy-4,5-*di*-(hydroxymethyl) pyridine hydrochloride.—Vitamin B<sub>6</sub> hydrochloride.—For structural formula see article on Pyridoxine.

It may be isolated from natural sources or prepared synthetically from ethoxy-acetylacetone and cyanoacetamide.

For tests and standards, see Section B.

**Actions and Uses.**—The nutritive and therapeutic value of pyridoxine hydrochloride has not been definitely established. It has been accepted by the Council for purposes of standardization and experimentation only.

**Dosage.**—A dose of 5 to 10 mg. daily is suggested.

BREWER & Co., INC.

**Solution Pyridoxine Hydrochloride: 50 mg. per cc. 10 cc. vials.**

ENDO PRODUCTS, INC.

**Solution Pyridoxine Hydrochloride: 1 cc. ampuls of 25 mg. and 50 mg. per cc. and 10 cc. vials of 50 mg. per cc.**

## LAKESIDE LABORATORIES, INC.

**Solution Pyridoxine Hydrochloride:** 50 mg. per cc. 5 cc. vials.

**Tablets Pyridoxine Hydrochloride:** 20 mg.

## MERCK &amp; Co., INC.

**Hexabione Hydrochloride (Powder):** 100 mg. bottles.  
U. S. trademark 377,657.

## SMITH-DORSEY COMPANY

**Tablets Pyridoxine Hydrochloride:** 1 mg.

## U. S. VITAMIN CORPORATION

**Solution Pyridoxine Hydrochloride:** 50 mg. per cc., 10 cc. vials. Preserved with 0.5 per cent chlorobutanol.

## THE UPJOHN COMPANY

**Solution Pyridoxine Hydrochloride:** 50 mg. in 2 cc. ampuls.

**Tablets Pyridoxine Hydrochloride:** 10 mg.

## WYETH, INCORPORATED

**Solution Pyridoxine Hydrochloride:** 50 mg. 1 cc. ampuls.

## Folic Acid Preparations

**FOLIC ACID.**—Folvite-Lederle.—Pteroylglutamic acid. —N-[4- } [(2-amino-4-hydroxy-6-pteridyl)methyl]amino } benzoyl] glutamic acid.

For tests and standards, see Section B.

**Actions and Uses.**—Folic acid is effective in bringing about a response of the blood, similar to that obtained with liver extract, in pernicious anemia, sprue, and nutritional macrocytic anemia. It also controls the diarrhea in sprue, but probably does not prevent or cause improvement in the spinal cord lesions in pernicious anemia; these are helped by liver extract. Therefore, folic acid should be used at this time only as an adjunct to liver therapy for the treatment of pernicious anemia.

**Dosage.**—5 to 10 mg. daily by mouth. (This is a preliminary estimate.) It may be administered by intramuscular injection, but in ordinary cases there is no advantage.

## AMERICAN PHARMACEUTICAL Co., INC.

**Tablets Folic Acid:** 5 mg.

## KREMERS-URBAN Co.

**Tablets Folic Acid:** 5 mg.

LEDERLE LABORATORIES, DIVISION AMERICAN CYANAMIDE CO.

**Elixir Folvite:** 5 mg. per 4 cc., 125 cc. bottles.

**Solution Sodium Folvite:** 15 mg. per cc. ampuls.

**Tablets Folvite:** 5 mg.

R. J. STRASENBURGH CO.

**Tablets Folic Acid:** 5 mg.

### Ascorbic Acid Preparations

**ASCORBIC ACID-U. S. P.—Cebione-Merck.—Vitamin C.**—"When dried in a vacuum desiccator over sulfuric acid for 3 hours, contains not less than 99 per cent of  $C_6H_8O_6$ ." U. S. P.

For description and standards see the U. S. Pharmacopeia under Ascorbic Acid and Ascorbic Acid Tablets.

Ascorbic Acid is quite stable; but in impure preparations and in many natural products the vitamin oxidizes on exposure to air or light, and such products should be preserved in an oxygen-free atmosphere protected from light.

Acceptance of tablets of ascorbic acid will be limited to 10, 25, 50 and 100 mg. of ascorbic acid per tablet.

*Actions and Uses.*—See article, Ascorbic Acid.

*Dosage.*—The optimum daily intake of ascorbic acid for an infant appears to be approximately 30 mg., and for an adult approximately 75 mg. Under certain conditions, notably pregnancy and lactation, the requirement of the adult may be as high as 100 or 150 mg.

When pharmacologic preparations are prescribed, the protective dose for infants is 10 mg. daily, and the therapeutic dose is 30 to 50 mg. daily. The protective dose for adults is 25 mg. daily and the therapeutic dose is 100 to 150 mg. daily. Each 1 mg. is equivalent to 20 international units of vitamin C. No evidence exists that ten-fold increases exert detrimental effects.

ABBOTT LABORATORIES

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

AMERICAN PHARMACEUTICAL CO., INC.

**Ascorbic Acid (Crystals):** 30 Gm. and 150 Gm. packages.

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

GEORGE A. BREON & COMPANY, INC.

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

BUFFINGTON'S INC.

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

BURROUGHS WELLCOME & CO., INC.

**Tabloid Ascorbic Acid:** 25 mg. and 100 mg.

COLE CHEMICAL Co.

**Tablets Ascorbic Acid:** 25 mg. and 100 mg.

R. E. DWIGHT & COMPANY

**Tablets Ascorbic Acid:** 50 mg. and 100 mg.

ENDO PRODUCTS, INC.

**Tablets Ascorbic Acid:** 10 mg., 25 mg., 50 mg. and 100 mg.

THE HARROWER LABORATORY, INC.

**Tablets Ascorbic Acid:** 100 mg.

INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY, INC.

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

McKESSON & ROBBINS, INC.

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

MEAD JOHNSON & COMPANY

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

MERCK & Co., INC.

**Cebione (*Crystals*):** 1.0 Gm. bottles.

U. S. trademark 318,171.

THE WM. S. MERRELL COMPANY

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

E. S. MILLER LABORATORIES, INC.

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

NATIONAL DRUG COMPANY

**Tablets Ascorbic Acid:** 25 mg. and 100 mg.

PARKE, DAVIS & COMPANY

**Solution of Ascorbic Acid:** 50 mg. per cc. 2 cc. glaseptic ampuls. Each cubic centimeter contains 50 mg. of ascorbic acid and 0.1 per cent of sodium bisulfite added as a preservative.

**Tablets Ascorbic Acid:** 25 mg. and 100 mg.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Tablets Ascorbic Acid:** 50 mg.

PREMO PHARMACEUTICAL LABORATORIES, INC.

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

SCHIEFFELIN & Co.

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

CARROLL DUNHAM SMITH PHARMACAL COMPANY

**Tablets Ascorbic Acid:** 100 mg.

SMITH-DORSEY COMPANY

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

E. R. SQUIBB & SONS

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

WINTHROP-STEARNs, INC.

**Tablets Ascorbic Acid:** 50 mg. and 100 mg.

U. S. VITAMIN CORPORATION

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

THE UPJOHN COMPANY

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

WALKER VITAMIN PRODUCTS, INC.

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

**Vitamin C Drops:** 15 cc. bottles with dropper. Each cc. contains 150 mg. of ascorbic acid, 0.25 cc. of water and 0.003 cc. orange oil, three parts of propylene glycol to one of glycerine.

WARREN-TEED PRODUCTS COMPANY

**Tablets Ascorbic Acid:** 25 mg., 50 mg. and 100 mg.

WYETH, INCORPORATED

**Tablets Ascorbic Acid:** 25 mg. and 100 mg.

**SODIUM ASCORBATE INJECTION-U. S. P.—**

"A sterile solution of sodium ascorbate ( $\text{Na}_2\text{H}_7\text{O}_6$ ) in water for injection. It contains not less than 95 per cent and not more than 115 per cent of the labeled amount of Ascorbic Acid  $\text{C}_6\text{H}_8\text{O}_6$ ." U. S. P.

For description and standards see the U. S. Pharmacopeia under Sodium Ascorbate Injection.

*Actions and Uses.*—Sodium ascorbate possesses the activity of ascorbic acid and is preferred when parenteral therapy is indicated.

*Dosage.*—Same as for ascorbic acid.

BARRY BIOLOGICAL LABORATORY, DIVISION OF BARRY LABORATORIES, INC.

**Solution Sodium Ascorbate:** 50 mg. per cc. 2 cc. ampuls. Each 2 cc. contains sodium ascorbate equivalent to 100 mg. of ascorbic acid.

GEORGE A. BREON & COMPANY, INC.

**Solution Sodium Ascorbate:** 50 mg. per cc. 2 cc. ampuls. Each 2 cc. contains sodium ascorbate equivalent to 100 mg.

(2,000 international units) ascorbic acid in sterile aqueous solution.

**Solution Sodium Ascorbate:** 50 mg. per cc. 10 cc. ampuls.

ENDO PRODUCTS, INC.

**Solution Sodium Ascorbate:** 50 mg. per cc. 2 cc. ampuls. Each cubic centimeter contains sodium ascorbate equivalent to 50 mg. of ascorbic acid, stabilized with the equivalent of 0.08 per cent sulfurous acid.

**Solution Sodium Ascorbate:** 50 mg. per cc. 5 cc. and 10 cc. ampuls. Each cubic centimeter contains sodium ascorbate equivalent to 100 mg. of ascorbic acid, stabilized with the equivalent of 0.08 per cent sulfurous acid.

LINCOLN LABORATORIES, INC.

**Solution Sodium Ascorbate:** 100 mg. per cc., 2 cc. and 5 cc. ampuls.

THE WM. S. MERRELL Co.

**Solution Sodium Ascorbate:** 100 mg. per cc., 2 cc. ampuls.

WILLIAM H. RORER

**Solution Sodium Ascorbate:** 100 mg. 1 cc. ampuls. Each cc. contains sodium ascorbate equivalent to 100 mg. (2,000 international units) ascorbic acid and thiourea 0.01 per cent in sterile aqueous solution.

### Vitamin D Preparations or Preparations Giving Vitamin D Effect

**COD LIVER OIL WITH VIOSTEROL** (See under Vitamins A and D Preparations).

**HALIBUT LIVER OIL WITH VIOSTEROL** (See under Vitamins A and D Preparations).

**SYNTHETIC OLEOVITAMIN D-U. S. P.**—Viosterol in Oil. (Applying only to Activated Ergosterol in Oil.) Irradiated Ergosterol in Oil.—“A solution of activated ergosterol, or activated 7-dehydro-cholesterol, in an edible vegetable oil. Synthetic Oleovitamin D contains in each Gm. not less than 10,000 U. S. P. units of vitamin D.

Synthetic Oleovitamin D must be labeled to indicate whether it contains activated ergosterol (*Vitamin D<sub>2</sub>* or *Viosterol*) or whether it contains activated 7-dehydro-cholesterol (*vitamin D<sub>3</sub>*).” U. S. P. Preparations listed under the title, Viosterol in Oil, contain activated ergosterol.

For description and standards see the U. S. Pharmacopeia under Synthetic Oleovitamin D.

*Actions and Uses.*—See article, Vitamin D.

*Dosage.*—Daily prophylactic dose for the average infant, 5 drops (approximately 0.1 cc.); for the premature and rapidly growing infant, 15 drops (0.31 cc.); daily curative dose, 15 to 20 drops (0.31 to 0.41 cc.); in severe cases, doses in excess of 20 drops may be given. The marketed preparations are accompanied by a standard dropper designed to deliver 3 drops to the minim.

*Preparation.*—

Viosterol in Oil is prepared by either of the following methods:

(a) Irradiation of a solution of purified ergosterol by ultraviolet rays under a determined distance and intensity for a definite length of time, under reflux in an inert atmosphere. After irradiation the solution is concentrated and the majority of the unchanged ergosterol is removed. The remaining solvent is distilled in an inert atmosphere and the irradiated ergosterol is dissolved in a known weight of vegetable oil. The resulting oil solution is adjusted by admixture of a bland vegetable oil so that the final product when assayed by the U. S. P. method has a vitamin D potency of not less than 10,000 U. S. P. units per Gm.

U. S. patents 1,680,818 (August 14, 1928; expired) and 1,871,136 (August 9, 1932; expires 1949) by license of the Wisconsin Alumni Research Foundation.

(b) Activation of purified ergosterol by low velocity electrons, after which the activated ergosterol is separated and dissolved in vegetable oil. The resulting solution is adjusted by admixture of a bland vegetable oil so that the final product when assayed by the U. S. P. method has a vitamin D potency of not less than 10,000 U. S. P. units per Gm.

Manufactured by General Mills, Inc., Special Commodities Division, under license agreement with E. I. du Pont de Nemours & Company. U. S. patent 2,117,100 (May 10, 1938; expires 1955).

#### ABBOTT LABORATORIES

**Solution Viosterol in Oil:** 5 cc., 20 cc. and 50 cc. bottles. Viosterol in sesame oil.

#### AMERICAN PHARMACEUTICAL Co., INC.

**Solution Viosterol in Oil:** 10 cc. and 50 cc. bottles. Viosterol in vegetable oil.

#### INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY, INC.

**Solution Viosterol in Oil:** 10 cc. and 60 cc. bottles. Viosterol in neutral vegetable oil.

#### McKESSON & ROBBINS, INC.

**Solution Viosterol in Oil:** 10 cc. and 60 cc. bottles. Viosterol in neutral vegetable oil.

#### MEAD JOHNSON & COMPANY

**Solution Viosterol in Oil:** 10 cc. and 50 cc. bottles. Viosterol in corn oil.



**PARKE, DAVIS & COMPANY**

**Solution Viosterol in Oil:** 5 cc. and 50 cc. bottles. Viosterol in corn oil.

**E. R. SQUIBB & SONS**

**Solution Viosterol in Oil:** 5 cc., 20 cc. and 50 cc. bottles. Viosterol in corn oil.

**VITAMIN D<sub>2</sub>.—Drisdol-Winthrop-Stearns.**—9,10-Ergostatetraene- (18:10, 5:6, 7:8, 22:23)-ol-3. For structural formula see the article on Vitamin D.

Vitamin D<sub>2</sub> may be prepared by ultraviolet irradiation of ergosterol in a suitable solvent or by electronic bombardment of the compound: it is not identical with the vitamin D which predominates in fish liver oils and which is called vitamin D<sub>3</sub>. A method of preparation of vitamin D<sub>2</sub> is given in Addendum 1936 to the British Pharmacopeia, 1932, page 20. The crystals have a potency of 40 units of vitamin D (U. S. P.) per microgram. (For methods of assay see U. S. P. XIII, p. 723.)

For tests and standards, see Section B.

*Actions and Uses.*—See article for vitamin D.

**WINTHROP-STEARN, INC.**

**Capsules Drisdol Concentrated Solution in Oil:** 5 minims. Each capsule contains 1.25 mg. of Drisdol and has a potency of 50,000 units of vitamin D (U. S. P.).

**Solution Drisdol in Propylene Glycol:** 5 cc., 10 cc. and 50 cc. bottles. Each 1 cc. contains 0.25 mg. of drisdol and has a potency of 10,000 units of vitamin D (U. S. P.) per gram. The propylene glycol used in the preparation of this product complies with the standards for propylene glycol-N. N. R.

*Dosage.*—Average daily dose: 2 drops dissolved in total ration of modified or whole milk. If administered in water, gruel, etc., 4 drops daily for the average infant, and up to 15 drops daily for the premature or rapidly growing infant. Daily curative dose: 15 to 20 drops. The product is marketed with a special dropper delivering 250 U. S. P. units of vitamin D per drop.

U. S. patent 1,902,785 (March 21, 1933; expires 1950) and 2,030,792 (Feb. 11, 1936; expires 1953) and by license of the Wisconsin Alumni Research Foundation under U. S. patents 1,680,818 (Aug. 14, 1928; expired) and 1,871,136 (Aug. 9, 1932; expires 1949). U. S. trademark 33,661.

**Vitamins A and D Preparations**

**CONCENTRATED OLEOVITAMIN A AND D.**  
**U. S. P.**—“Fish liver oil, or fish liver oil diluted with an edible vegetable oil, or a solution of Vitamin A and D concentrates in fish liver oil or in an edible vegetable oil. The Vitamin A obtained from natural (animal) sources and the Vitamin D may be obtained from natural (animal) sources or may be synthetic

oleovitamin D. Concentrated Oleovitamin A and D contains in each gram not less than 50,000 and not more than 65,000 U. S. P. units of Vitamin A, and not less than 10,000 and not more than 13,000 U. S. P. units of Vitamin D." *U. S. P.*

For description and standards see the U. S. Pharmacopeia under Concentrated Oleovitamin A and D and Concentrated Oleovitamin A and D Capsules.

*Actions, Uses and Dosage.*—See under Vitamin A and D preparations.

McKESSON & ROBBINS, INC.

**Concentrated Oleo Vitamins A and D:** 6 cc. vials. A concentrate of vitamins A and D prepared from cod liver oil, the concentrate containing not less than 60,000 U. S. P. units of vitamin A and not less than 10,000 U. S. P. units of vitamin D per gram.

WALKER VITAMIN PRODUCTS, INC.

**Drops Concentrated Oleo Vitamin A-D:** Each gram contains not less than 62,500 U. S. P. units of vitamin A and not less than 10,000 U. S. P. units of vitamin D. Natural esters of vitamin A (distilled from fish liver and vegetable oils) plus activated ergosterol in refined corn oil. Flavored with cinnamon.

**BURBOT LIVER OIL.**—The oil extracted from the livers of the Burbot (*Lota maculosa*), family *Gadidae*. It is biologically assayed to have a potency of not less than 4,880 units of vitamin A (U. S. P.) per gram and of not less than 640 units of vitamin D (U. S. P.) per gram.

For tests and standards, see Section B.

*Actions and Uses.*—Same as those of cod liver oil. See article Vitamins A and D Preparations.

*Dosage.*—Prophylactic, 1 cc. (40 drops) daily; or as prescribed by the physician. The product is marketed with a dropper designed to deliver about 2.5 drops to the cubic centimeter.

BURBOT LIVER PRODUCTS Co.

**Burbot Liver Oil (Rowell):** 60 cc. and 240 cc. bottles.

**Capsules Burbot Liver Oil (Rowell):** 0.52 cc. minims, adjusted to have a potency of not less than 2,215 units of vitamin A (U. S. P.) and 315 units of vitamin D (U. S. P.) per capsule.

**COD LIVER OIL-U. S. P.**—"The partially destearinated fixed oil obtained from fresh livers of *Gadus morrhua* Linné and other species of the family *Gadidae*. Cod Liver Oil contains in each Gm. at least 850 U. S. P. units of Vitamin A and at least 85 U. S. P. Units of Vitamin D. Cod Liver Oil may be flavored by the addition of not more than 1 per cent of any one or any mixture of flavoring substances recognized in the U. S. Pharmacopeia." *U. S. P.*

For description and standards see the U. S. Pharmacopeia under Cod Liver Oil.

*Actions, Uses and Dosage.*—See article, Vitamins A and D Preparations.

**COD LIVER OIL WITH VIOSTEROL.** — Viosterol dissolved in cod liver oil, to adjust it to the potency of not less than 850 units (U. S. P.) of vitamin A per Gm., 360 units (U. S. P.) of vitamin D per Gm.

*Actions and Uses.*—See general article, Viosterol. Cod liver oil with viosterol is proposed for use in conditions in which it is desired to supplement the administration of vitamin A with that of a relatively large amount of vitamin D.

*Dosage.*—For infants and young children, 2.5 to 3.3 cc. daily; for adults and in severe cases doses up to 7 cc. or more are given.

*Preparation.*—

Cod liver oil with viosterol is prepared by addition of irradiated ergosterol to cod liver oil in such proportion that the finished product will have a potency of not less than 850 units (U. S. P.) of vitamin A per Gm. and not less than 360 units (U. S. P.) of vitamin D per Gm.

#### MEAD JOHNSON & COMPANY

**Cod Liver Oil with Viosterol:** 118 cc. and 473 cc. bottles. Each 1 Gm. has a potency of not less than 1,800 U. S. P. units of vitamin A and of not less than 400 U. S. P. units of vitamin D.

#### PARKE, DAVIS & COMPANY

**Cod Liver Oil with Viosterol:** 90 cc. and 480 cc. bottles. Each 1 Gm. has a potency of not less than 2,000 U. S. P. units of vitamin A and of not less than 400 U. S. P. units of vitamin D.

#### E. R. SQUIBB & SONS

**Cod Liver Oil with Viosterol:** 90 cc. and 480 cc. bottles. Each 1 Gm. has a potency of not less than 2,000 U. S. P. units of vitamin A and of not less than 440 U. S. P. units of vitamin D.

**COD LIVER OIL CONCENTRATE (LIQUID).** — A concentrate of the nonsaponifiable fraction of cod liver oil dissolved in cod liver oil or in neutral vegetable oil. Preparations of cod liver oil concentrate having a vitamin A potency of not less than 50,000 and not more than 65,000 units per gram and a vitamin D potency of not less than 5,000 and not more than 6,500 units per gram will be considered for acceptance.

*Actions and Uses.*—Cod liver oil concentrate (liquid) possesses properties similar to those of cod liver oil so far as these depend on the vitamin content of the latter.

*Dosage.*—Prophylactic: For liquids: 6 to 12 drops daily. For capsules: 1 or 2 capsules daily.

Cod liver oil concentrate is made under U. S. patent 1,690,091 (October 30, 1928; expired) or under U. S. patent 1,984,858 (December 18, 1934; expires 1951).

CLINADOL COMPANY, INC.

**Cod Liver Oil Concentrate:** 60 cc. bottles, packaged with a dropper designed to deliver approximately 1 minim per drop. An extract of the nonsaponifiable fraction of cod liver oil in maize oil, to which has been added saccharin (3 in 10,000) and oil of cassia, 2 per cent. Each 1 Gm. of the concentrate has a potency of not less than 60,000 U. S. P. units of vitamin A and of not less than 6,000 U. S. P. units of vitamin D.

U. S. trademark 279,325.

INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY, INC.

**Concentrate of Vitamins A and D from Cod Liver Oil in Vegetable Oil:** bulk. Each 1 Gm. has a potency of not less than 60,000 U. S. P. units of vitamin A and of not less than 8,500 U. S. P. units of vitamin D.

**Concentrate of Vitamins A and D from Cod Liver Oil in Vegetable Oil:** 6 cc. and 60 cc. bottles. Each packaged with a dropper designed to supply 48 drops per gram. Each drop has a potency of not less than 1,250 U. S. P. units of vitamin A and not less than 175 U. S. P. units of vitamin D.

**Capsules Concentrate of Vitamins A and D from Cod Liver Oil in Vegetable Oil:** 0.195 cc. Each capsule has a potency of not less than 5,000 U. S. P. units of vitamin A and not less than 1,000 U. S. P. units of vitamin D.

WHITE LABORATORIES, INC.

**Cod Liver Oil Concentrate Liquid:** bulk. A cod liver oil concentrate dissolved in cod liver oil having a potency of not less than 55,000 U. S. P. units of vitamin A and of not less than 5,500 U. S. P. units of vitamin D per gram.

**Cod Liver Oil Concentrate Liquid:** 6 cc., 30 cc. and 60 cc. vials, packaged with a dropper designed to supply in each 2 drops (0.062 cc.) a potency of not less than 3,120 U. S. P. units of vitamin A and of not less than 312 U. S. P. units of vitamin D.

**Capsules Cod Liver Oil Concentrate:** 0.195 cc. Each capsule has a potency of not less than 5,000 U. S. P. units of vitamin A and of not less than 500 U. S. P. units of vitamin D.

**COD LIVER OIL CONCENTRATE TABLETS.** — Cod liver oil in the form of tablets having a potency of not less than 3,120 U. S. P. units of vitamin A and of not less than 312 U. S. P. units of vitamin D.

*Actions and Uses.*—Cod Liver Oil Concentrate Tablets possess properties similar to cod liver oil so far as these depend on the fat soluble vitamin content of the latter.

*Dosage.*—Two to six tablets daily.

INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY, INC.

**Tablets Concentrate of Vitamins A and D from Cod Liver Oil:** Each tablet has a potency of not less than 3,150 U. S. P. units of vitamin A and of not less than 315 U. S. P. units of vitamin D.

WHITE LABORATORIES, INC.

**Tablets Cod Liver Oil Concentrate:** Each tablet has a potency of not less than 3,120 U. S. P. units of vitamin A and of not less than 312 U. S. P. units of vitamin D.

**HALIBUT LIVER OIL WITH VIOSTEROL. — Haliver Oil with Viosterol—Abbott and Parke, Davis.**—Halibut liver oil to which has been added sufficient viosterol (activated ergosterol) to assure a potency of not less than 10,000 U. S. P. units of vitamin D per gram.

*Actions and Uses.*—The same as those for cod liver oil. See general article, Vitamins A and D Preparations.

*Dosage.*—For infants, 8 to 10 drops (about 0.16 cc. to 0.20 cc.) daily; for premature and rapidly growing infants, 15 drops (about 0.3 cc.) daily; for older children, 15 to 20 drops (0.3 to 0.42 cc.) daily; for adults, especially nursing and expectant mothers, 20 drops (about 0.42 cc.) or more daily. The marketed preparation is accompanied by a special dropper designed to deliver a certain number of drops to the minim.

ABBOTT LABORATORIES

**Haliver Oil with Viosterol:** 5 cc., 20 cc. and 50 cc. bottles.

U. S. trademark 294,692.

**Soluble Gelatin Capsules Haliver Oil with Viosterol:** 0.09 cc. Each capsule supplies 5,000 U. S. P. units of vitamin A and 1,000 U. S. P. units of vitamin D.

INTERNATIONAL VITAMIN DIVISION, IVES-CAMERON COMPANY, INC.

**Halibut Liver Oil with Viosterol in Oil:** 10 cc. and 60 cc. bottles.

**Soluble Gelatin Capsules Halibut Liver Oil with Viosterol in Oil:** 0.195 cc. Each capsule supplies 5,000 U. S. P. units of vitamin A and 1,700 U. S. P. units of vitamin D.

McKESSON & ROBBINS, INC.

**Halibut Liver Oil with Viosterol in Oil:** 6 cc. and 60 cc. bottles.

**Soluble Gelatin Capsules Halibut Liver Oil with Viosterol in Oil:** 0.195 cc. Each capsule supplies 8,500 U. S. P. units of vitamin A and 1,700 U. S. P. units of vitamin D.

MEAD JOHNSON & COMPANY

**Viosterol in Halibut Liver Oil:** 10 cc. and 50 cc. bottles.

PARKE, DAVIS & COMPANY

**Haliver Oil with Viosterol:** 5 cc., and 50 cc. bottles.

**Soluble Gelatin Capsules Haliver Oil with Viosterol:** Each capsule supplies 5,000 U. S. P. units of vitamin A and 1,000 U. S. P. units of vitamin D.

U. S. trademark 294,692.

**PERCOMORPH LIVER OIL.—Oleum Percomorphum.**

—A mixture containing the fixed oils obtained from the fresh livers of the percomorph fishes, principally *Xiphias gladius*, *Pneumatophorus diego*, *Thunnus thynnus* and *Stereolepis gigas*—sometimes also *Neothunnus macropterus*, *Katsuwonus pelamis*, *Sarda chiliensis*, *Germo alalunga*, *Thunnus orientalis*, *Scomber scombrus*, *Seriola dorsalis*, *Lutianus campechanus*, *Epinephelus morio*, *Roccus lineatus*, *Cynoscion nobilis*, *Eriscion macdonaldi*, *Epinephelus analogus*, *Stereolepis ishinagi* and *Sphyaena argentea*, containing not more than 50 per cent of other fish liver oil. It is biologically assayed to have a potency of not less than 60,000 units of vitamin A (U. S. P.) per gram and of not less than 8,500 units of vitamin D (U. S. P.) per gram.

For tests and standards, see Section B.

**Actions and Uses.**—Same as those of cod liver oil. See general article, Vitamins A and D Preparations.

**Dosage.**—Prophylactic, for normal infants, 10 drops daily; curative, and in severe conditions, to 20 drops daily. The product is marketed with a dropper designed to deliver 44 drops to the cc.

AMERICAN PHARMACEUTICAL CO., INC.

**Codanol Percomorph Liver Oil 50% with Viosterol:** 10 cc. and 50 cc. A source of vitamin A and D in which not less than 50 per cent of the vitamin content is derived from the liver oils of percomorph fishes with viosterol added. Each gram contains not less than 60,000 U. S. P. units of vitamin A and 8,500 U. S. P. units of vitamin D.

FLINT, EATON & COMPANY

**Oleum Percomorphum:** 8 cc. bottle.

MEAD JOHNSON & COMPANY

**Oleum Percomorphum with Other Fish-Liver Oils and Viosterol:** A blend of liver oils of percomorph fishes, viosterol and other fish livers. A source of vitamin A and D in which not less than 50 per cent of the vitamin content is derived from

the livers of percomorph fishes. Each gram contains not less than 60,000 U. S. P. units of vitamin A and 8,500 U. S. P. units of vitamin D.

**Oleum Percomorphum with Other Fish-Liver Oils and Viosterol:** 10 cc. and 50 cc. bottles.

**Capsules Oleum Percomorphum with Other Fish-Liver Oils and Viosterol:** Each capsule contains 83 mg. of oleum percomorphum with other fish liver oils and viosterol and supplies a potency of 5,000 U. S. P. units of vitamin A and 700 U. S. P. units of vitamin D.

**SHARK LIVER OIL.**—The oil extracted from the livers of the shark, mainly of the variety *Hypoprion brevirostris* (lemon), but any or all of the following varieties may be included: *Odontaspis littoralis* (sand), *Isurus punctatus* (mackerel), *Triakis semifasciatus* (leopard), *Sphyrna zygaena* (hammerhead), *Carcharias obscurus* (dusky), *Ginglymostoma cirratum* (nurse), *Carcharias milberti* (white) and *Carcharias limbatus* (black tip). It is biologically assayed and has a potency of not less than 16,500 units of vitamin A (U. S. P.) per gram and of not less than 40 units of vitamin D (U. S. P.) per gram; the latter is insignificant if taken according to directions.

For tests and standards, see Section B.

**Actions and Uses.**—See the general article, Vitamin A and D Preparations.

**Dosage.**—One capsule, or about 0.52 cc., daily.

## Vitamin K Preparations

**MENADIONE-U. S. P.—Kayquinone-Abbott.—Thyloquinone-Squibb.** — 2-Methyl-1,4-Naphthoquinone. — “When dried over sulfuric acid in a vacuum desiccator for 4 hours, contains not less than 98.5 per cent of  $C_{11}H_8O_2$ .” It may be prepared by oxidizing 2-methylnaphthalene with chromic acid.

For description and standards see the U. S. Pharmacopeia under Menadione and Menadione Tablets.

**Actions and Uses.**—A synthetic naphthoquinone derivative having physiologic properties of vitamin K. See the general article, Vitamin K.

**Dosage.**—From 1 to 2 mg. daily or as prescribed by the physician. In cases of prothrombin deficiency due to bile obstruction, bile salts should be administered with menadione.

The acceptance of tablets menadione is limited to 1 and 2 mg. of menadione per tablet; the acceptance of capsules menadione is limited to 1 and 2 mg. of menadione per capsule, and the acceptance of ampul solution for parenteral use is limited to 1 and 2 mg. of menadione per cc.

**“Caution.**—Menadione powder is irritating to the respiratory tract and to the skin, and an alcoholic solution has vesicant properties.”

ABBOTT LABORATORIES

**Tablets Kayquinone:** 1 mg.

**Capsules Kayquinone:** 1 mg.

U. S. trademark 382,006.

GEORGE A. BREON & COMPANY, INC.

**Tablets Menadione:** 2 mg.

R. E. DWIGHT & COMPANY

**Capsules Menadione:** 2 mg.

ENDO PRODUCTS, INC.

**Solution Menadione in Oil:** 2 mg. per 2 cc. 2 cc. ampuls.  
Each cc. contains 1 mg. menadione in corn oil.

**Tablets Menadione:** 1 mg. and 2 mg.

LAKESIDE LABORATORIES, INC.

**Capsules Menadione in Oil:** 2 mg.

**Solution Menadione in Oil:** 2 mg. 1 cc. ampuls. Contains  
0.5 per cent of chlorobutanol as preservative in sesame oil.

MCNEIL LABORATORIES

**Capsules Menadione in Oil:** 2 mg.

MERCK & CO., INC.

**Menadione (Powder).**

E. S. MILLER LABORATORIES, INC.

**Solution Menadione in Oil:** 1 mg. per cc. 1 cc. ampuls.  
Each cc. contains 1 mg. of menadione with benzocaine 2 per  
cent. Preserved with 0.5 per cent cresol.

**Tablets Menadione:** 1 mg.

SHARP & DOHME, INC.

**Solution Menadione in Oil:** 2 mg. per cc. 1 cc. ampuls  
in peanut oil.

**Tablets Menadione:** 1 mg.

SMITH-DORSEY COMPANY

**Tablets Menadione:** 1 mg.

E. R. SQUIBB & SONS

**Solution Thyloquinone in Oil:** 2 mg. per cc. 1 cc. ampuls.  
Each cc. contains 2 mg. of thyloquinone in corn oil.



**Capsules Thyloquinone in Oil:** Each brown gelatin capsule contains 1 mg. of thyloquinone in corn oil.

U. S. trademark 379,351.

U. S. VITAMIN CORPORATION

**Capsules Menadione:** 1 mg. and 2 mg.

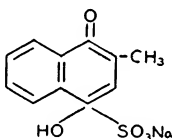
**Solution Menadione in Oil:** 1 mg. per cc. 1 cc. ampuls. Each cc. contains 1 mg. of menadione in corn oil.

THE VALE CHEMICAL CO., INC.

**Tablets Menadione:** 2 mg.

### Vitamin K Preparations

**MENADIONE SODIUM BISULFITE - U. S. P. — Hykinone-Abbott.**—Menadione Bisulfite.—“Contains not less than 49 per cent of menadione ( $C_{11}H_8O_2$ )”—U. S. P. Menadione Sodium Bisulfite has the following structural formula:



It may be prepared by the interaction of menadione and sodium bisulfite to form the addition product.

For description and standards see the U. S. Pharmacopeia under Menadione Sodium Bisulfite and Menadione Sodium Bisulfite Injection.

**Actions and Uses.**—Menadione sodium bisulfite is used for essentially the same conditions as is menadione, which possesses the physiologic properties of vitamin K. Unlike menadione it is soluble in water, and stable aqueous solutions may be prepared. Since this material is water soluble, oral administration is effective without the use of bile salts.

**Dosage.**—It may be administered subcutaneously, intramuscularly or intravenously, the average daily dose being 0.5 to 2 mg. During administration of the drug the prothrombin level of the blood should be followed, especially when there appears to be need of an additional dose during a twenty-four hour period.

ABBOTT LABORATORIES

**Solution Hykinone:** 72 mg., 10 cc. ampuls. Each 10 cc. contains Menadione U. S. P. 72 mg., and Sodium Bisulfite 27.5 mg. in an aqueous solution made isotonic with sodium chloride.

U. S. patent 2,367,302. U. S. trademark 383,789.

## THE WM. S. MERRELL COMPANY

**Solution Menadione Sodium Bisulfite:** 3.84 mg. per cc. 1 cc. ampuls. Each cubic centimeter contains the equivalent of 2 mg. of menadione, stabilized with 0.05 per cent sodium bisulfite.

**Tablets Menadione Sodium Bisulfite:** 3.84 mg.

U. S. Patent number 2,331,808.

**VITAMIN K<sub>1</sub>.**—2-Methyl-3-Phtyl-1,4-Naphthoquinone.—

It may be isolated from natural sources or prepared by condensing 2-methyl-1,4-naphthoquinone with the suitable phtyl derivative.

For tests and standards, see Section B.

*Actions and Uses.*—See the general article Vitamin K. It has been suggested that vitamin K<sub>1</sub> has a more prolonged effect than menadione.

*Dosage.*—From 4 mg. to 10 mg. by mouth, with or without bile salts. Intravenous dose for adults may be as much as 10 mg. dispersed in dextrose solution. For newborn infants a dose of 0.25 mg. may be administered intravenously.

## MERCK &amp; Co., INC.

**Vitamin K<sub>1</sub>:** 1 Gm., 5 Gm. and 25 Gm. ampuls.

**Mixed Vitamin Preparations**

**HEXAVITAMIN U. S. P.**—"Hexavitamin Capsules and Tablets contain in each capsule or tablet not less than 5,000 U. S. P. units of vitamin A from natural (animal) sources, 400 U. S. P. units of vitamin D from natural (animal) sources, or as activated ergosterol or activated 7-dehydrocholesterol 75 mg. of ascorbic acid, 2 mg. of thiamine hydrochloride, 3 mg. of riboflavin and 20 mg. of nicotinamide."—*U. S. P. XIII.*

For description and standards see the U. S. Pharmacopeia under capsulae Hexavitaminarum and Tabellae Hexavitaminarum.

*Actions, Uses and Dosage.*—For prophylaxis and treatment of conditions arising from deficiency of vitamins A and D and ascorbic acid, thiamine, riboflavin and nicotinic acid. See articles on the various vitamins concerned.

## THE WM. S. MERRELL COMPANY

**Tablets Hexavitamin-U. S. P. XII:** Each tablet contains 2,500 U. S. P. units of vitamin A, 200 U. S. P. units of vitamin D, 1 mg. of thiamine hydrochloride, 1.5 mg. of riboflavin, 37 mg. of ascorbic acid and 10 mg. of nicotinamide. This formula is one-half the strength specified by the current (Thirteenth) Revision of the United States Pharmacopoeia. Manufactured in accordance with the formula specified in the previous (Twelfth) Revision of the United States Pharmacopoeia.

WALKER VITAMIN PRODUCTS, INC.

**Capsules Hexavitamin:** Each capsule contains 5,000 U. S. P. units of vitamin A, 400 U. S. P. units of vitamin D, 2 mg. of thiamine, 3 mg. of riboflavin, 75 mg. of ascorbic acid and 20 mg. of niacinamide.

**COD LIVER OIL WITH VIOSTEROL** (See under Vitamins A and D Preparations).

**PERCOMORPH LIVER OIL** (See under Vitamins A and D Preparations).

**TRIASYN B** (See under Mixed Vitamin B Components.)

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# NEW AND NONOFFICIAL REMEDIES

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## SECTION B

### TESTS AND STANDARDS

#### INTRODUCTION

Section B of New and Nonofficial Remedies contains chemical and physical descriptions, and methods for the identification and standardization of Council-accepted drugs for which official standards are not available. These methods have been developed jointly by the A. M. A. Chemical Laboratory and the firms submitting preparations to the Council. The Tests and Standard in this section are arranged alphabetically according to the non-protected (generic) names of the drugs.

The test solutions required in the qualitative and quantitative tests have been designated by their official names and, unless otherwise stated, the strengths are those specified in the U. S. P. XIII. Percentage, where it is used for specifying strengths of solutions, means "weight over volume"; exceptions are stated when they occur.

All the common tests, i.e. for absence of heavy metals, sulfates and chlorides, are performed as described in detail in U. S. P. XIII. Less common tests are given either in the individual monographs or in the references cited.

The A. M. A. Chemical Laboratory currently is engaged in a critical examination of the analytical methods appearing in this Section of New and Nonofficial Remedies. Criticism from other analysts will be appreciated.

**ABSORBABLE GELATIN SPONGE.**—Gelfoam-Upjohn.—A sterile absorbable water-insoluble gelatin base sponge.

Gelfoam is obtained by foaming a specially prepared skin gelatin solution, which is then dried in air and subsequently sterilized by dry heat at 149° C.

Gelfoam is a light, nearly white, nonelastic, tough, porous matrix that may be cut into any shape or size. It shows no tendency to disintegrate even with relatively rough handling. A piece of Gelfoam may be rapidly wetted by working it vigorously between moistened fingers, and it will then readily imbibe water. A 10 mm. cube of Gelfoam weighing approximately 9 mg. will take up approximately fifty times its weight of water or forty-five times its weight of well agitated oxalated whole blood. Gelfoam will withstand dry heat at 149° C. The residue on ignition shall not exceed 20 mg. per gram of Gelfoam.

Place a 50 mg. piece of Gelfoam in a beaker of distilled water. Squeeze the Gelfoam out gently between the fingers until the sponge is thoroughly wet, care being taken not to break the tissue. Lift from the water and remove the excess water with absorbent paper. Place the wetted sample in a 150 cc. stoppered flask which contains 100 cc. of a 1 per cent solution of pepsin N.F. in tenth-normal hydrochloric acid previously warmed to 37° C. Maintain at a temperature of 37° C., and agitate gently and continuously until digestion is complete. The average digestion time is less than thirty minutes.

**ACETPYROGALLOL.**— $C_{12}H_{12}O_6$ .—M. W. 252.22—Triacetyl pyrogallol.

Acetpyrogallol is a white, crystalline powder, melting at 165° C. It is insoluble in water, but soluble with decomposition in warm aqueous alkalis. It is incompatible with alkalis, strong acids and oxidizing agents.

**AFENIL-Bilhuber-Knoll.**— $C_4H_{16}CaCl_2N_8O_4$ .—F. W. 351.2.—A molecular compound of calcium chloride and urea,  $CaCl_2 \cdot 4(NH_2)_2CO$ .

Afenil occurs as colorless crystals; non-hygroscopic; very soluble in water.

The calcium content of Afenil is determined by precipitating with ammonium oxalate in the usual way and weighing as calcium oxide. The urea content of Afenil is determined by an estimation of nitrogen by the Kjeldahl method.

**ALLYL BARBITURIC ACID.**— $C_{11}H_{16}N_2O_3$ .—M. W. 224.25.—5-Isobutyl-5-allyl barbituric acid.

Allyl barbituric acid occurs as a white, crystalline, odorless powder, with a slightly bitter taste; completely soluble in ethyl alcohol, acetone, chloroform, ether, ethyl acetate and glacial acetic acid; slightly soluble in cold water; sparingly soluble in boiling water and petroleum ether; and insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. It melts at 138-139° C. It is stable in air.

Place about 0.3 Gm. of allyl barbituric acid in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. normal sodium hydroxide and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in 10 cc. of diluted ammonia solution; to the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in 5 cc. of diluted ammonia solution. Boil about 0.5 Gm. of allyl barbituric acid with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of strongly alkaline vapors. Place about 1 Gm. of allyl barbituric acid in a 25 cc. glass stoppered cylinder, add 10 cc. of water, shake for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of acetic acid and 0.5 cc. of bromine T.S.: an immediate discoloration occurs. To the other portion add 0.1 cc. potassium permanganate T.S.: a yellow color appears immediately, turning to brown.

Dissolve about 0.1 Gm. of allyl barbituric acid in 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Boil about 0.5 Gm. of allyl barbituric acid with 50 cc. of water for two minutes: no odor develops; cool and filter: separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate T.S. (*sulfate*); no coloration or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Ash about 1 Gm. of allyl barbituric acid, accurately weighed: the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm. of allyl barbituric acid, accurately weighed, in 25 cc. of previously neutralized alcohol; dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide, using thymolphthalein T.S. as an indicator; the amount

of tenth-normal sodium hydroxide consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of *isobutyl-allyl* barbituric acid.

**ALUMINUM HYDROXIDE GEL-N. N. R.**—An aqueous suspension containing not less than 3 per cent nor more than 4.2 per cent of aluminum oxide ( $\text{Al}_2\text{O}_3$ .—F. W. 101.94), chiefly in the form of aluminum hydroxide ( $\text{Al}(\text{OH})_3$ .—F. W. 77.99). Flavoring, sweetening and preservatives may be added.

See also standards of the U. S. Pharmacopeia under Aluminum Hydroxide Gel.

Aluminum hydroxide gel occurs as a white or light gray suspension which may settle out to some extent or form a semisolid on standing but which liquefies on shaking. The specific gravity at 25 C. is from 1.030 to 1.042.

Transfer about 5 Gm. of aluminum hydroxide gel to a glass container and add 10 cc. of diluted hydrochloric acid: the solution is clear and colorless within ten minutes; to this solution add 8 cc. of diluted ammonia solution: a flocculent precipitate appears which is insoluble in excess diluted ammonia solution but soluble in sodium hydroxide solution. To about 5 Gm. of aluminum hydroxide gel in an Erlenmeyer flask add 10 cc. of sodium hydroxide T.S. and boil: the fumes do not turn moistened red litmus paper to blue (*ammonia*).

Dissolve 10 Gm. of aluminum hydroxide gel in 10 cc. of diluted hydrochloric acid and boil. Cool, dilute to 250 cc. and filter if necessary. To 10 cc. add 1 cc. of barium chloride T.S. and allow to stand for ten minutes: the turbidity is not greater than that produced by 0.2 cc. of fiftieth-normal sulfuric acid in 10 cc. of water.

The  $\text{pH}$  at 25 C. of aluminum hydroxide gel is between 6.4 and 7.2. Dissolve 2.5 Gm. of the gel in 5 cc. of diluted sulfuric acid and boil: the solution meets the U. S. P. test for arsenic. Dissolve 10 Gm. of aluminum hydroxide gel in 10 cc. of diluted sulfuric acid: the resultant solution conforms to the U. S. P. test for heavy metals.

Transfer 25 Gm. of aluminum hydroxide gel, accurately weighed, to an Erlenmeyer flask, add 25 cc. of distilled water and 0.2 cc. of potassium chromate T.S. Titrate with tenth-normal silver nitrate to a faint pink color: the chlorine content is not greater than 0.35 per cent.

Transfer about 3 Gm. of aluminum hydroxide gel, accurately weighed, to an Erlenmeyer flask, dilute to 30 cc. and maintain at 37.5 C. Titrate with tenth-normal hydrochloric acid during forty minutes, adding the acid in 0.5 cc. portions toward the end of the titration, using bromophenol blue T.S. as indicator: the volume of tenth-normal acid used is not more than 2,500 cc., nor less than 1,250 cc. per hundred Gm.

Transfer about 3 Gm. of aluminum hydroxide gel, accurately weighed, to a 250 cc. beaker and dilute to 100 cc. Add 10 cc. of diluted hydrochloric acid, heat to boiling and make the mixture alkaline to methyl red with diluted ammonia solution. Dilute to 200 cc., heat to boiling and wash four times by decantation. Filter and wash the precipitate free of chlorides with an aqueous solution containing 1 part of diluted ammonia solution in 25 parts of solution. Dry the precipitate and ignite at 900 C. to constant weight: the aluminum oxide content is not less than 3 nor more than 4.2 per cent.

**AMOBARBITAL.**— $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_3$ .—M. W. 226.27.—5-Isoamyl-5-ethylbarbituric acid.

Amobarbital occurs as a white crystalline, odorless powder, with a slightly bitter taste. It is completely soluble in alcohol and ether, very slightly soluble in cold water and insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. It melts at 156-158.5° C. (U. S. P. corr.)

Place 0.3 Gm. of amobarbital in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. sodium hydroxide T.S. and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions. To one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate

results, soluble in 10 cc. of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in 5 cc. of diluted ammonia solution. Boil 0.5 Gm. of amobarbital with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia.

Dissolve 0.1 Gm. of amobarbital in 1 cc. of sulfuric acid: the solution is colorless (*readily carbonized substance*). Boil 0.5 Gm. of amobarbital with 50 cc. of water for two minutes: no odor develops; cool and filter: separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate T.S. (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*).

Incinerate about 1 Gm. of amobarbital, accurately weighed: the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm. of amobarbital, accurately weighed, in 25 cc. of previously neutralized alcohol; dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide solution, using thymolphthalein T.S. as an indicator: the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of isoamyl ethylbarbituric acid.

**AMOBARBITAL SODIUM.**— $C_{11}H_{17}N_2NaO_3$ .—M. W. 248.26.—The monosodium salt of 5-isoamyl-5-ethylbarbituric acid.

Amobarbital sodium occurs as a white, friable, hygroscopic, odorless, granular powder with a slightly bitter taste; very soluble in water; freely soluble in alcohol, about 1 part in 1 part; practically insoluble in ether.

Dissolve about 0.5 Gm. of amobarbital sodium in 100 cc. of water, add an excess of diluted hydrochloric acid: collect the resultant isoamyl-ethylbarbituric acid on a filter, wash and dry: it melts at  $156-158.5^{\circ}C$ . (U. S. P. corr.) Incinerate about 1 Gm. of amobarbital sodium: the residue responds to tests for sodium carbonate. Boil about 0.5 Gm. of amobarbital sodium with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia. Dissolve about 0.3 Gm. of amobarbital sodium in 10 cc. of water and divide into two portions. To one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in an excess of strong ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in 5 cc. of diluted ammonia solution.

Dissolve about 0.5 Gm. of amobarbital sodium in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper: separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate T.S. (*chloride*); no turbidity on the addition of 1 cc. of barium nitrate T.S. (*sulfate*). To about 0.2 Gm. of amobarbital sodium in 25 cc. of water, add 1 cc. of diluted hydrochloric acid and filter through paper: the filtrate yields no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*). Add about 0.2 Gm. of amobarbital sodium to 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Transfer about 1 Gm. of amobarbital sodium, accurately weighed, to a glass stoppered cylinder, add 50 cc. of anhydrous ether, stopper and shake the contents for ten minutes; decant the supernatant liquid through filter paper, and repeat twice, using first 25 cc. and second 15 cc. of ether and utilizing the same filter; evaporate the combined filtrate to dryness in a tared beaker and dry to constant weight at  $100^{\circ}C$ : the residue does not exceed 0.2 per cent (*uncombined isoamylethylbarbituric acid*).

Dry about 1 Gm. of amobarbital sodium, accurately weighed, to constant weight at  $90^{\circ}C$ : The loss does not exceed 1 per cent. Transfer about 0.5 Gm. of amobarbital sodium, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by the addition of 10 cc. of diluted hydrochloric acid, extract with eight successive portions of ether, using 25 cc. each, evaporate the combined ethereal extracts to dryness in a stream of warm air and dry to constant weight at  $90^{\circ}C$ : The amount of isoamylethylbarbituric acid corresponds to not less than 90 per cent nor more than 91.6 per cent (theory 91.15 per cent), calculated to the dried substance. Transfer the acidulated aqueous portion

from the foregoing extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained add 5 cc. of sulfuric acid and heat cautiously until the excess of sulfuric acid has been volatilized; repeat twice, using 1 cc. of sulfuric acid each time, add about 0.5 Gm. of ammonium carbonate, ignite to constant weight and weigh as sodium sulfate: The percentage of sodium corresponds to not less than 8.9 per cent nor more than 9.5 per cent when calculated to the dried substance.

**AMPHETAMINE.**— $C_9H_{13}N$ .—M. W. 135.20.—*d,l*-1-Phenyl-2-aminopropane.—Racemic desoxynor-ephedrine.

Amphetamine occurs as a colorless, mobile liquid, boiling at 200-203 C., with slight decomposition. The specific gravity at 25 C. is 0.931. The vapor pressure at ordinary temperature is relatively high, and the substance possesses a strong basic odor and a burning taste. It is soluble in ether and alcohol and slightly soluble in water.

Place 1 Gm. of amphetamine in an Erlenmeyer flask, add 50 cc. of water and 5 cc. of 40 per cent sodium hydroxide solution, then add benzoyl chloride, 0.5 cc. at a time; shake the flask after each addition; add the benzoyl chloride until no more precipitate forms after an addition. Recrystallize the derivative twice from 50 per cent alcohol and dry the crystals, which melt at 134-135 C. The nitrogen content of the benzoyl derivative by the micro Dumas method is not less than 5.7 nor more than 5.95 per cent.

Transfer 0.5 Gm. of amphetamine, accurately weighed, to a tared weighing bottle and place on the steam bath for one hour. The residue is not more than 0.5 per cent (*nonvolatile compounds*). Dissolve 1 cc. of amphetamine in 10 cc. of liquid petrolatum U. S. P. (anhydrous): no turbidity is produced (*water*).

Suspend about 1 Gm. of amphetamine, accurately weighed, in 10 cc. of water and titrate with half-normal sulfuric acid, using methyl red T.S. as an indicator: the acid used corresponds to not less than 95 per cent nor more than 100 per cent of the base (1 cc. half-normal sulfuric acid is equivalent to 0.0675 Gm. of base).

Determine carbon, hydrogen and nitrogen by micro combustion methods. The carbon should be not less than 79.7 nor more than 80.2 per cent; the hydrogen, not less than 9.6 nor more than 9.9 per cent; and the nitrogen, not less than 10.2 nor more than 10.6 per cent.

**Benzedrine Inhaler-Smith, Kline and French.**—Each inhaler tube contains, at the time of packing, 0.25 Gm. amphetamine, 10 mg. menthol and aromatics.

**BENZEDRINE INHALER:** Transfer the filling to a Kjeldahl distillation flask, add 250 cc. of water and 1 Gm. of sodium hydroxide; distil 150 cc. into 25 cc. of tenth-normal sulfuric acid, titrate the excess acid with tenth-normal sodium hydroxide solution using methyl red T.S. as indicator. Each inhaler shall contain not less than 0.235 Gm. nor more than 0.275 Gm. per tube.

Transfer the solution from the titration to a separatory funnel, extract with 30 cc. of ether, transfer the aqueous layer to an Erlenmeyer flask, add 2 cc. of 40 per cent sodium hydroxide solution and a total of 1.5 cc. of benzoyl chloride, 0.5 cc. at a time, shaking the flask and contents thoroughly after each addition and allowing the reaction mixture to set for one hour before the next portion of benzoyl chloride is added; heat on a steam bath until the odor of benzoyl chloride has disappeared; remove the precipitate by filtration, wash with cold water and dry at 90° C.: the melting point is 130-135° C.

**AMPHETAMINE SULFATE.**— $C_{18}H_{28}N_2O_4S$ .—M. W. 368.48.—*d,l*-1-Phenyl-2-aminopropane sulfate.—Racemic desoxy-nor-ephedrine sulfate.

Amphetamine sulfate occurs as a white, odorless powder; freely soluble in water, slightly soluble in alcohol; insoluble in ether. A solution of 1 Gm. in 10 cc. of water has a pH between 5.0 and 6.0. Amphetamine sulfate melts above 300° C., with decomposition.



Place 1 Gm. of amphetamine sulfate in an Erlenmeyer flask, add 50 cc. of water and 5 cc. of 40 per cent sodium hydroxide solution; then add benzoyl chloride, 0.5 cc. at a time; shake the flask after each addition; add the benzoyl chloride until no more precipitate forms after an addition. Recrystallize the derivative twice from 50 per cent alcohol and dry the crystals, which melt at 134-135° C. The nitrogen content of the benzoyl derivative by the micro Dumas method is not less than 5.70 per cent nor more than 5.95 per cent.

Dry about 0.5 Gm. of amphetamine sulfate, accurately weighed, to constant weight at 100 C.: the loss does not exceed 1 per cent. Incinerate about 0.5 Gm. of amphetamine sulfate, accurately weighed: the residue is not more than 0.1 per cent.

Transfer 0.3 Gm. of amphetamine sulfate, accurately weighed, to a beaker and dissolve in 200 cc. of water and 2 cc. of normal hydrochloric acid. Boil and add 10 cc. of boiling 10 per cent barium chloride T.S. Allow to stand overnight, filter, wash, until free from chloride, ignite at low red heat to constant weight, cool, and weigh: the sulfate content is not less than 25.5 per cent nor more than 26.4 per cent.

Dissolve 0.25 Gm. of amphetamine sulfate, accurately weighed, in 25 cc. of water in a separatory funnel. Add 3 cc. of 10 per cent sodium hydroxide solution and extract with six 15 cc. portions of ether. Filter the ether extracts into a glass stoppered flask and shake with 20 cc. of tenth-normal sulfuric acid. Evaporate the ether on a steam bath; add one drop of methyl red T.S. and titrate the excess acid with tenth-normal sodium hydroxide solution: the amphetamine content is not less than 72 per cent nor more than 73.5 per cent.

**AMPROTROPINE PHOSPHATE.**— $C_{18}H_{32}NO_7P$ .—M. W. 405.42.—The phosphate of *d,l*-tropic acid ester of 3-diethylamino-2,2-dimethyl-1-propanol.

Amprotropine phosphate occurs as a white, crystalline powder, with a faint roseate odor and a bitter taste. It is freely soluble in water, slightly soluble in absolute alcohol and insoluble in chloroform and ether. The aqueous solution is acid to litmus. Amprotropine phosphate melts at 142° to 145° C. From aqueous solutions, alkali hydroxides precipitate the free base as a water-white oil, which does not solidify at ordinary temperatures.

Place about 0.01 Gm. of amprotropine phosphate in a porcelain dish, add a few drops of nitric acid, and evaporate to dryness on a water bath: a yellow residue results; cool, add a few drops of alcoholic potassium hydroxide solution: the mixture is a violet color.

Dry about 0.5 Gm. of amprotropine phosphate, accurately weighed, to constant weight at 100° C.: the loss in weight does not exceed 1 per cent. Incinerate about 0.5 Gm. of amprotropine phosphate, accurately weighed, in a platinum crucible: the residue does not exceed 0.1 per cent. Transfer about 0.5 Gm. of amprotropine phosphate to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the official method described in *Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, p. 27, paragraph 25: the percentage of nitrogen corresponds to not less than 3.3 per cent nor more than 3.6 per cent when calculated to the dried substance.

**AMYLSINE HYDROCHLORIDE**-Novocol. —  $C_{14}H_{22}O_2N_2.HCl$ .—M. W. 286.79.—2-*p*-Aminobenzoxy-1-*n*-amylaminoethane hydrochloride.

Amylsine Hydrochloride occurs as a fine, white, odorless powder which, when applied to the tongue, produces a bitter taste followed by a sense of numbness. It is soluble in water, sparingly soluble in ethanol and insoluble in ether, benzene and chloroform. An aqueous solution is acid to litmus. The free base separates as a solid from Amylsine Hydrochloride solutions on the addition of sodium hydroxide or carbonate T.S. but not with 5 per cent sodium bicarbonate solution. Amylsine Hydrochloride occurs in dimorphic forms. The form which crystallizes from amyl alcohol melts at 176° C., while the one crystallized from water melts at 153.5° C.; the free base melts at 65° C.

Dissolve 0.1 Gm. of Amylsine Hydrochloride in 50 cc. of water; to one 5 cc. portion add 1 cc. of silver nitrate T.S.: a white precipitate results, soluble in excess of diluted ammonia solution. To another 5 cc. portion add 0.5 cc. of diluted hydrochloric acid, 0.5 cc. of a 10 per cent solution of sodium nitrite and then 10 cc. of diluted ammonia solution containing 0.2 Gm. of betanaphthol: an orange precipitate results, soluble in ether. To a 2 cc. portion add 1 cc. of mercuric potassium iodide T.S.: a white precipitate results. To a 2 cc. portion add 2 cc. of trinitrophenol T.S.: a yellow precipitate results. Dissolve 0.1 Gm. of Amylsine Hydrochloride in 5 cc. of water, add 2 drops of sulfuric acid and 1 cc. of a saturated solution of sodium nitrite, and heat to 50° C.: a yellow oil separates (*distinction from butyn, cocaine, procaine and tetracaine*). Dissolve 0.1 Gm. of Amylsine Hydrochloride in 1 cc. of sulfuric acid; the solution is colorless (*readily carbonizable substances*). Saturate a solution of 0.1 Gm. in 10 cc. of water with hydrogen sulfide: no coloration or precipitation occurs (*salts of heavy metals*).

Transfer about 0.5 Gm. of Amylsine Hydrochloride, accurately weighed, to a tared platinum dish and dry at 100 C. for six hours: the loss in weight does not exceed 3 per cent. Incinerate about 0.5 Gm. of Amylsine Hydrochloride, accurately weighed: the ash does not exceed 0.1 per cent. Transfer a sample of Amylsine Hydrochloride, previously dried and accurately weighed, to a Kjeldahl flask and digest with sulfuric acid in the presence of 0.1 Gm. of selenium; dilute, make alkaline with 40 per cent sodium hydroxide solution, distil into standard acid and titrate the excess acid with standard alkali: the nitrogen content is not greater than 9.8 nor less than 9.4 per cent. Transfer about 0.5 Gm. of Amylsine Hydrochloride, previously dried and accurately weighed, to a 250 cc. beaker and dissolve in 100 cc. of water. Heat to boiling and add 1 cc. of nitric acid and 20 cc. of silver nitrate T.S., digest on the steam bath for three hours, filter, wash, dry and weigh the precipitate: the chlorine content is not greater than 12.5 nor less than 12.0 per cent.

**ANTHRALIN.**— $C_{14}H_{10}O_3$ .—M. W. 226.22.—1,8,9-Anthra-triol.

Anthralin occurs as an odorless and tasteless, yellow, crystalline powder, which is readily soluble in chloroform; soluble in acetone, benzene and pyridine; slightly soluble in alcohol, ether and glacial acetic acid; and insoluble in water. It is soluble in sodium hydroxide T.S., yielding a yellow to orange colored solution possessing greenish fluorescence. Alkaline solutions of anthralin rapidly oxidize in air, lose fluorescence and become a deep orange-red. The melting point of anthralin is from 175° to 181° C.

Dissolve about 0.1 Gm. of anthralin in 10 cc. of alcohol, and 0.1 cc. of diluted ferric chloride T.S.: a greenish brown color results. Add a few crystals of anthralin to 2 cc. of sulfuric acid: an orange-yellow color results (*1,8-dihydroxyanthraquinone gives a scarlet color*).

Dissolve 0.1 Gm. of anthralin in 10 cc. of warm acetone: the solution is clear; pour the solution into 200 cc. of water: a yellow precipitate results. Add 5 cc. of sodium hydroxide T.S. and mix: the precipitate dissolves and the yellow colored solution rapidly changes to orange and finally to red.

Add about 0.5 Gm. of anthralin to a mixture of 3 cc. of anhydrous pyridine and 3 cc. of acetic anhydride and boil about fifteen minutes. Pour the mixture on crushed ice, collect the precipitate and recrystallize twice from glacial acetic acid: the melting point of the yellow needle shaped crystals of triacetyl anthralin obtained is from 208° to 210° C., with sublimation.

Add 0.5 Gm. of anthralin to 10 cc. of water, mix and filter: the filtrate is neutral; separate portions of the filtrate yield no turbidity on the addition of silver nitrate T.S., barium nitrate T.S. or ammonium sulfide T.S., and no color on the addition of ferric chloride T.S.

Ignite 0.5 Gm. of anthralin: the ash is negligible.

Transfer 0.1 Gm. of anthralin, accurately weighed, to a beaker, add 75 cc. of acetone and warm to dissolve the solid. While the solution is hot, add 10 cc. of silver ammonium nitrate solution (dissolve 3 Gm. of silver nitrate in 120 cc. of water and add 10 cc. of 10 per cent

ammonium hydroxide solution), mix and allow to stand at room temperature for two hours. Filter through a suitable Gooch crucible (or sintered glass filter). Wash the beaker and precipitate with ether, acetone, then about 300 cc. of ammoniacal ammonium nitrate solution (dissolve 15 Gm. of ammonium nitrate in 300 cc. of water and add 10 cc. of strong ammonia solution) and finally wash with acetone. Place the filter in the beaker used for the precipitation of silver, add 10 cc. of water and 10 cc. of nitric acid and heat to near boiling to facilitate solution of the silver. Add enough water to cover the filter and boil gently for twenty minutes. Add 0.5 Gm. of chloride free decolorizing charcoal, mix, let stand for ten minutes and filter while hot through paper. Rinse the beaker and crucible with hot water and finally wash the paper and residue with hot water; combine the filtrate and washings. Cool and titrate with tenth-normal ammonium thiocyanate, using 5 cc. of ferric ammonium sulfate T.S., acidified with nitric acid, as the indicator. Each cubic centimeter of tenth-normal ammonium thiocyanate is equivalent to 0.01079 Gm. of silver. The amount of silver precipitated, calculated from the titration, is not less than 1.35 times and not more than 1.45 times the amount of anthralin taken.

**ANTIMONY THIOGLYCOLLAMIDE.**— $C_6H_{12}N_3O_3S_3Sb$ .—M. W. 392.13.—The triamide of antimony thioglycollic acid,  $Sb(S.CH_2CO.NH_2)_3$ .

Antimony thioglycollamide is a white, crystalline, odorless powder. It is soluble in about 200 parts of water, somewhat soluble in alcohol and insoluble in ether. It melts at about  $139^\circ C.$  (uncorrected).

Dissolve a few crystals of antimony thioglycollamide in 5 cc. of water and add a drop of ferric chloride T.S.: a transient blue color appears. Boil about 0.1 Gm. of antimony thioglycollamide with 5 cc. of sodium hydroxide T.S.: ammonia is evolved. Dissolve about 0.1 Gm. of antimony thioglycollamide in 25 cc. of warm water, add a few drops of diluted hydrochloric acid and pass in hydrogen sulfide: an orange precipitate is produced.

Dissolve 0.2 Gm. of antimony thioglycollamide in 5 cc. of hydrochloric acid, add 10 cc. of freshly prepared stannous chloride solution and allow to stand 30 minutes: no brownish tint or precipitate is visible if viewed from above over a white surface (*arsenic*). A blank test should be carried out, using the same quantities of reagents.

Weigh accurately from 0.2 to 0.3 Gm. of antimony thioglycollamide, dissolve it in about 100 cc. of warm water, add 1 cc. of diluted hydrochloric acid, pass in hydrogen sulfide until precipitation is complete and allow to stand 30 minutes. Collect the antimony sulfide in a weighed Gooch crucible; wash it successively with water containing hydrogen sulfide, alcohol, ether, carbon disulfide, alcohol and ether; dry the residue at  $100^\circ C.$ ; and weigh. The antimony sulfide obtained corresponds to not less than 30 per cent of antimony.

**APROBARBITAL.**— $C_{10}H_{14}N_2O_3$ .—M. W. 210.23.—5-Allyl-5-isopropylbarbituric acid.

Aprobarbital occurs as a fine white, odorless crystalline powder, with a slightly bitter taste; completely soluble in alcohol, chloroform and ether; very slightly soluble in cold water; insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Aprobarbital melts at  $140^\circ$  to  $141.5^\circ C.$

Place about 0.3 Gm. of aprobarbital in a glass stoppered cylinder, add a mixture of 1 cc. of normal sodium hydroxide solution and 5 cc. of water, shake contents for 1 minute. filter through paper and divide into two portions. To one portion add 1 cc. of mercury bichloride T.S.: a white precipitate results, soluble in an excess of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in an excess of diluted ammonia solution. Boil about 0.5 Gm. of Aprobarbital with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia. Dissolve about 0.1 Gm. of aprobarbital in 1 cc. of sulfuric acid: not

more than a slight yellow color results. Place about 1 Gm. of aprobarbital in a 25 cc. glass stoppered cylinder, add 10 cc. of water, shake the mixture for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of acetic acid and 0.5 cc. of bromine T.S.: an immediate discoloration occurs. To the other portion add 0.1 cc. of potassium permanganate T.S.: a yellow color appears immediately, turning to brown.

Boil about 0.5 Gm. of aprobarbital with 50 cc. of water for two minutes: no odor develops; cool and filter: separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate T.S. (*sulfate*); no coloration or precipitation on saturation with hydrogen sulfide (*salts of heavy metals*). Ash about 1 Gm. of aprobarbital, accurately weighed: there is not more than 0.1 per cent residue. Dissolve about 0.5 Gm. of aprobarbital, accurately weighed, in 25 cc. of previously neutralized alcohol. Dilute with an equal volume of water previously boiled to remove carbon dioxide and titrate with tenth-normal sodium hydroxide solution, using thymolphthalein T.S. as an indicator: the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent allyl isopropylbarbituric acid.

**APROBARBITAL SODIUM.**— $C_{10}H_{13}N_2NaO_3$ .—M. W. 232.22.—The monosodium salt of 5-allyl-5-isopropylbarbituric acid.

Aprobarbital sodium is a white microcrystalline, hygroscopic, odorless powder, with a slightly bitter taste; very soluble in water; very slightly soluble in alcohol; practically insoluble in ether. An aqueous solution of aprobarbital sodium is alkaline to litmus.

Dissolve about 0.5 Gm. of aprobarbital sodium in 100 cc. of water, add an excess of diluted hydrochloric acid; collect the resultant allyl isopropyl barbituric acid on a filter, wash and dry at 90° C.: it melts at 139 to 140° C. Incinerate about 1 Gm. of aprobarbital sodium: the residue responds to tests for sodium carbonate. Boil about 0.5 Gm. of aprobarbital sodium with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia. Dissolve about 0.3 Gm. of aprobarbital sodium in 10 cc. of water and divide into two portions. To one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in an excess of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in an excess of diluted ammonia solution.

Dissolve about 0.5 Gm. of aprobarbital sodium in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper: separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate T.S. (*chloride*); no turbidity on the addition of 1 cc. of barium nitrate T.S. (*sulfate*). To about 0.2 Gm. of aprobarbital sodium in 25 cc. of water, add 1 cc. of diluted hydrochloric acid and filter through paper: the filtrate yields no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*). Add about 1 Gm. of aprobarbital sodium to 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Transfer about 1 Gm. of aprobarbital sodium, accurately weighed, to a glass stoppered cylinder, add 50 cc. of anhydrous ether, stopper and shake for ten minutes: decant the supernatant liquid through filter paper and repeat twice, using 25 cc. and 15 cc. portions, respectively, of ether, utilizing the same filter. Evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 90° C.: the residue does not exceed 0.2 per cent (*uncombined allylisopropyl barbituric acid*).

Dry about 1 Gm. of aprobarbital sodium, accurately weighed, at 90° C. for forty-eight hours: the loss in weight should not be less than 4.5 per cent nor more than 7.5 per cent. Transfer about 0.5 Gm. of aprobarbital sodium, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by addition of 10 cc. of diluted hydrochloric acid; extract with eight successive portions of ether of 25 cc. each, evaporate the combined ethereal extractions to dryness in a stream of warm air and dry to constant weight at 90° C.: the amount of allylisopropyl barbituric acid corresponds to not less than 90 per cent

nor more than 91 per cent, calculated to the dried substance. Transfer the acidified aqueous portion from the foregoing immiscible solvent extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained add 5 cc. of sulfuric acid; heat *cautiously* until the excess of sulfuric acid has been volatilized; repeat twice, using portions of 1 cc. each of sulfuric acid each time; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight, and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 9 per cent nor more than 10 per cent when calculated to the dried substance.

**BENZESTROL.**— $C_{20}H_{26}O_2$ .—M. W. 298.41.—Octofollin.—2,4-Di-(*p*-hydroxyphenyl)-3-ethyl hexane.

Benzestrol is an odorless, white, crystalline powder which melts at from 152 to 166 C. It is readily soluble in acetone, ether, ethanol, methanol and sodium hydroxide T.S.; soluble in vegetable oils; moderately soluble in glacial acetic acid; slightly soluble in benzene, chloroform, petroleum ether and dilute ethanol; practically insoluble in water and in dilute mineral acids.

Dissolve 10 mg. of benzestrol in 2 cc. of concentrated sulfuric acid: a pale yellow color is produced which persists on dilution with water (*distinction from diethylstilbestrol, which yields an orange color.*) Add a few drops of 50 per cent solution of antimony pentachloride in dry alcohol-free chloroform to a very dilute solution of benzestrol in the same solvent: a green colored solution which rapidly changes to brown is produced (*distinction from diethylstilbestrol, which yields a red or bluish red color.*)

Add 1 cc. of benzoyl chloride to 0.1 Gm. of benzestrol contained in a test tube; heat and maintain gentle boiling for five minutes; cool, add 20 cc. of sodium hydroxide T.S. and shake the mixture thoroughly until a white solid mass separates. Filter, wash the precipitate with water and recrystallize twice from hot ethanol: the melting point of the 2,4-di-(*p*-hydroxyphenyl)-3-ethylhexane dibenzoate obtained is from 118° to 120° C.

Dissolve 0.1 Gm. of benzestrol in 5 cc. of ether: the solution is clear and colorless. Dissolve 0.1 Gm. of benzestrol in 5 cc. of previously neutralized 75 per cent ethanol solution: the solution is neutral.

Dry an accurately weighed specimen of benzestrol at 100° C. for one hour: the loss in weight does not exceed 0.1 per cent. Ignite an accurately weighed specimen of benzestrol after the addition of 0.5 cc. of sulfuric acid: the residue is not more than 0.05 per cent.

Transfer 0.1 Gm. of benzestrol, accurately weighed, to a 100 cc. volumetric flask, add 15 cc. of normal sodium hydroxide and 30 cc. of distilled water; shake to dissolve the benzestrol, then dilute to the mark with distilled water. Transfer exactly 20 cc. of the solution to a 250 cc. iodine flask fitted with an accurately ground stopper; add 10 cc. of freshly distilled carbon tetrachloride and 10 cc. of 10 per cent hydrochloric acid. Wet the stopper with distilled water; insert the stopper and shake the flask and contents to dissolve the precipitated benzestrol in the carbon tetrachloride layer. Place 2 to 3 cc. of water around the stopper and cautiously remove it, avoiding loss of contents on release of compressed vapor. Rinse down the neck and walls of the flask with 3 to 5 cc. of distilled water. Add exactly 20 cc. of tenth-normal bromide-bromate solution down the wall of the flask and quickly insert the stopper, avoiding possible loss of bromine vapor. Shake the flask and contents thoroughly for several minutes. Place about 5 cc. of 10 per cent potassium iodide solution around the stopper and let the flask stand in the dark for 30 to 40 minutes at 25° to 30° C. At the end of this period allow the sodium iodide solution to enter the flask, avoiding loss of vapor from within; place 3 to 5 cc. of distilled water around the stopper and allow it to rinse in the sodium iodide solution. Stopper the flask tightly and shake thoroughly. Let the mixture stand for five minutes and then titrate with tenth-normal sodium thiosulfate solution, shaking the mixture thoroughly after each addition of the reagent. The end point of the titration is reached when on addition of a fraction of a drop of the sodium thiosulfate solution followed by thorough shaking of the mixture the pink color of iodine in the carbon tetrachloride layer disappears. Each cubic centimeter of

tenth-normal bromide-bromate solution is equivalent to 3.730 mg. of benzestrol: the amount of benzestrol found is not less than 99 per cent nor more than 101 per cent.

**BENZETHONIUM CHLORIDE.**— $C_{27}H_{42}ClNO_2 \cdot H_2O$ .—M. W. 466.09.—[p-(2-Methyl-4,4-dimethyl pentano-2)(phenoxy-ethoxy-ethyl)]-dimethylbenzylammonium chloride monohydrate.

Benzethonium chloride appears as colorless, odorless crystals possessing a very bitter taste. It may be recrystallized from a chloroform solution, by the addition of ether, in the form of very thin plates, which may assume a hexagonal shape. These crystals possess a high birefringence, parallel extinction and positive elongation and are biaxial with refractive indexes of 1.580 and 1.560. These crystals and the original material sinter slightly on the hot stage at 120 C. and melt at 164-166 C. The  $pH$  of a 1 per cent solution of benzethonium chloride is between 4.8 and 5.5.

Mineral acids and many salt solutions precipitate benzethonium chloride from solutions more concentrated than 2 per cent, as an oil which crystallizes on drying and has the same properties as benzethonium chloride. A solution of benzethonium chloride yields a flocculent white precipitate with soap solutions. To 1 cc. of a 1 per cent solution of benzethonium chloride add 2 cc. of ethanol, 0.5 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S.: a flocculent white precipitate appears, which is insoluble in diluted nitric acid but soluble in diluted ammonia solution.

Dissolve 0.1 Gm. of benzethonium chloride in 1 cc. of sulfuric acid, add 0.1 Gm. of sodium nitrate and heat on the steam bath for three minutes. Dilute the solution to 10 cc., add 0.5 Gm. of granulated zinc and warm for ten minutes. Cool, add 0.2 Gm. of sodium nitrite to 1 cc. of the clear liquid and add this mixture to 0.02 Gm. of G salt (sodium 2-naphthol-6,8-disulfonate) in 1 cc. of strong ammonia solution: the solution turns orange-red and a brown precipitate may appear.

Transfer approximately 1 Gm. of benzethonium chloride, accurately weighed, to a tared platinum dish and dry in an oven at 100° C. to constant weight: the loss in weight is not less than 3.5 nor more than 4.2 per cent. Ignite the residue: the weight of ash is not more than 0.1 per cent.

Transfer approximately 2 Gm. of benzethonium chloride, accurately weighed, to a 100 cc. flask; dissolve in 30 cc. of water; add 10 cc. of nitric acid and 50 cc. of tenth-normal silver nitrate; dilute to the mark, mix well and filter through a dry paper. To 25 cc. of the filtrate add 1 cc. of 10 per cent ferric ammonium sulfate and titrate with tenth-normal ammonium thiocyanate: the chlorine content is not less than 7.6 nor more than 8.0 per cent, calculated to the dried substance.

Transfer an accurately weighed sample of benzethonium chloride to a Kjeldahl flask, and digest with sulfuric acid in the presence of selenium; cool, dilute with water, make alkaline with 40 per cent sodium hydroxide, distill the ammonia into the standard acid solution and titrate the excess acid: the nitrogen content is not less than 2.6 nor more than 3.1 per cent.

Dissolve approximately 1 Gm. of benzethonium chloride, accurately weighed, in distilled water to make 100 cc. of solution. Transfer exactly 25 cc. of this solution to a 100 cc. volumetric flask, add 5 cc. of buffer solution (260 Gm. of sodium acetate and 250 cc. of 36 per cent acetic acid mixed with distilled water to make 1 liter) and exactly 50 cc. of 0.01 molar potassium ferricyanide (weigh exactly 3.2922 Gm. of potassium ferricyanide crystals, dried for one hour at 100° C., and dissolve in distilled water to make 1 liter). Make up to 100 cc. with distilled water; mix well and allow to stand for 1 hour with occasional shaking. Filter through a dry No. 50 Whatman paper and discard the first 20 cc. of filtrate. Transfer exactly 50 cc. of the subsequent filtrate to a 250 cc. flask. Add 5 cc. of potassium iodide T.S., and 5 cc. of diluted hydrochloric acid. After one minute add 10 cc. of 10 per cent zinc sulfate solution and titrate with 0.01 normal sodium thiosulfate, using starch T.S. as the indicator near the endpoint. Conduct a blank determination at the same time with the same quantities of reagents; omit the benzethonium chloride and titrate

with 0.01 normal sodium thiosulfate as directed. The factor 0.01398 multiplied by the difference in volumes of sodium thiosulfate solution used for the blank and for the determination gives the amount of benzethonium chloride monohydrate in the aliquot taken: the amount of benzethonium chloride monohydrate found is not less than 97 per cent nor more than 103 per cent.

**BISMUTH ARSPHENAMINE SULFONATE.**—Sulfarsphenamine Bismuth.—The sodium salt of a bismuth derivative of arspenamine methylene sulfonic acid (the exact structural formula of which has not been established) with inorganic salts. It contains approximately 13 per cent of arsenic and 24 per cent of bismuth.

Bismuth arspenamine sulfonate is a brownish-yellow amorphous powder readily soluble in water, yielding a yellow solution which is slightly alkaline to litmus.

Add 2 cc. of diluted hydrochloric acid to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: a white opalescence appears and dissolves almost immediately; a heavy white gelatinous precipitate develops in two minutes. Add 1 cc. of diluted nitric acid to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: the solution gradually turns brown and yields a precipitate. Add 1 cc. of trinitrophenol T.S. to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: no apparent reaction takes place (*distinction from silver arspenamine and bismuth potassium tartrate*). Bubble hydrogen sulfide through a 1 per cent solution of bismuth arspenamine sulfonate: the solution darkens immediately but no precipitate is formed. Add 5 cc. of hydrogen peroxide solution to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: the solution is at first turbid, then becomes a deep reddish brown with formation of a precipitate. Add 1 cc. of mercuric potassium iodide T.S. to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: the solution yields a greenish-yellow opalescence, which in turn assumes a dirty green color on standing. Add drop by drop 2 cc. of a 40 per cent sodium hydroxide solution to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: the solution gradually darkens without any formation of precipitate. Add 0.5 cc. of a 2 per cent silver nitrate solution to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: a dark red solution is produced (*distinction from arspenamine*). Add 1 cc. of bromine T.S. to 5 cc. of a 1 per cent solution of bismuth arspenamine sulfonate: The solution yields a greenish brown precipitate (*distinction from sulf-arsphenamine, neoarsphenamine and arspenamine*). Add 0.5 Gm. of zinc dust and 5 cc. of diluted hydrochloric acid to 0.1 Gm. of bismuth arspenamine sulfonate in a test tube and at the mouth of the tube hold a strip of filter paper moistened with 5 per cent cadmium chloride solution: the paper turns yellow in four minutes.

Transfer about 0.4 Gm. of bismuth arspenamine sulfonate, accurately weighed, to a Kjeldahl flask, add 2 cc. of sulfuric acid and heat carefully; add 2 cc. of nitric acid a drop at a time, continue heating until brown fumes cease to be given off, cool and add water to make 120 cc.; if a white crystalline precipitate appears, dissolve it with a few drops of hydrochloric acid; transfer to a 250 cc. beaker, add 7 Gm. of tartaric acid, neutralize with strong ammonia water and add 10 cc. of magnesia mixture followed by 20 cc. strong ammonia solution, allow to stand 12 hours, filter through a hard surfaced filter paper and wash the precipitate with 50 cc. of 2.5 per cent diluted ammonia solution, puncture the filter, transfer the precipitate into a 250 cc. beaker with washings, then add just sufficient hydrochloric acid to dissolve the precipitate, filter, wash the filter well with water, neutralize the filtrate with strong ammonia solution; add 1 cc. of magnesia mixture and 20 cc. of strong ammonia solution; allow to stand 12 hours, filter, using a prepared Gooch crucible; wash with 2.5 per cent diluted ammonia solution; dry at 100° C.; ignite at 700° C. for three hours; cool in a desiccator and weigh as magnesium pyroarsenate and calculate to arsenic: the arsenic content is not less than 12.50 per cent nor more than 13.50 per cent. Transfer about 0.25 Gm. of bismuth arspenamine sulfonate, accurately

weighed, to an Erlenmeyer flask. Add 5 cc. of diluted sulfuric acid followed by 1 Gm. of powdered potassium permanganate, and 10 cc. of sulfuric acid in small portions; add just sufficient hydrogen peroxide solution to dissolve the brown precipitate; add 50 cc. of water; boil for 20 minutes; cool to 70° C.; saturate with hydrogen sulfide, then stopper the flask and allow it to stand for 12 hours; filter, using a prepared Gooch crucible; wash the precipitate with water, warm ammonium polysulfide, methyl alcohol, carbon bisulfide and acetone in the order named; dry at 100° C.; cool in a desiccator and weigh as bismuth sulfide ( $\text{Bi}_2\text{S}_3$ ); calculate to bismuth: the percentage of bismuth found corresponds with the percentage of arsenic found multiplied by 1.86 (factor As to Bi in  $\text{C}_{21}\text{H}_{21}\text{O}_{12}\text{As}_3\text{Na}_3\text{S}_2\text{N}_3\text{Bi}_2$ ) plus or minus 0.5 per cent.

**BISMUTH CAMPHOCARBOXYLATE.**— $\text{C}_{33}\text{H}_{46}\text{Bi}_2\text{O}_{11}$ .—F. W. 1036.7—A basic bismuth salt of camphocarboxylic acid having the probable formula  $(\text{C}_{10}\text{H}_{15}\text{OCOO})_2\text{BiO}(\text{Bi}(\text{C}_{10}\text{H}_{15}\text{OCOO})\text{OH})$ .

Bismuth camphocarboxylate occurs as a white powder having the odor of camphor. It is insoluble in water but soluble in ether, benzene and vegetable oils.

Heat 1 Gm. of bismuth camphocarboxylate in 30 cc. of water containing 3 cc. of hydrochloric acid, add diluted ammonia solution until resulting solution is alkaline to litmus, filter and wash the precipitate with 10 cc. of water; to the filtrate add hydrochloric acid until just acid to litmus, evaporate on the steam bath until the volume is reduced one half, cool, filter and dry the crystals: the crystals melt at 127° C. Dissolve 0.1 Gm. of the crystals in 5 cc. of alcohol, add a drop of diluted ferric chloride solution (ferric chloride T.S. diluted 1 to 5): a green color results. Dissolve the precipitate (obtained from the treatment with diluted ammonia solution) in diluted hydrochloric acid and pass in hydrogen sulfide: a black precipitate forms. Suspend 0.2 Gm. of bismuth camphocarboxylate in 10 cc. of boiling water and add 2 Gm. of sodium hydrosulfite: a black precipitate forms.

Add 5 cc. of sodium hydroxide T.S. and about 0.2 Gm. of aluminum wire to about 0.2 Gm. of bismuth camphocarboxylate; heat gently: the vapors do not turn red litmus blue (*nitrate*). Suspend 0.25 Gm. in 30 cc. of water, add 4 cc. diluted nitric acid, boil, cool, filter and add 1 cc. of silver nitrate T.S.: no more turbidity is produced than in the U. S. P. test for chlorides using 0.1 cc. of fiftieth normal hydrochloric acid (*chloride*). Suspend 0.1 Gm. in 30 cc. of water, add 4 cc. of diluted hydrochloric acid, boil, cool, filter, add 1 cc. of barium chloride T.S. and dilute to 50 cc.: no turbidity is produced in ten minutes (*sulfate*). Add 2 cc. of nitric acid to 2 Gm. of bismuth camphocarboxylate in a porcelain crucible, evaporate to dryness on the steam bath, ignite, add 5 cc. of hydrochloric acid and 10 cc. of a saturated solution of stannous chloride in hydrochloric acid: the mixture does not darken in thirty minutes (*arsenic*). Ignite 3 Gm. of bismuth camphocarboxylate in a quartz crucible, cool, add drop by drop just enough nitric acid to dissolve the residue when warmed, pour the acid solution into 100 cc. of distilled water, evaporate to 30 cc., filter if necessary and divide into 5 cc. portions. To one portion add an equal quantity of diluted sulfuric acid: the liquid does not become cloudy (*lead*). To another portion add an excess of diluted ammonia solution: the liquid does not exhibit a bluish tint (*copper*). To another portion add 0.5 cc. of diluted hydrochloric acid: a precipitate insoluble in an excess of hydrochloric acid and soluble in diluted ammonia solution is not formed (*silver*).

Transfer about 0.2 Gm. of bismuth camphocarboxylate, accurately weighed, to an Erlenmeyer flask, add 1 Gm. of powdered potassium permanganate and then 5 cc. of diluted sulfuric acid, allow to stand ten minutes, add 10 cc. of sulfuric acid in small portions, allow to stand 15 minutes, decolorize with hydrogen peroxide, add 25 cc. of water, boil for 15 minutes, pass in hydrogen sulfide until the bismuth is completely precipitated, filter through a prepared Gooch crucible, wash with water, alcohol, chloroform and ether in this order, dry in an oven for 30 minutes at 100° C., cool in a desiccator and weigh; repeat the washing with chloroform and ether and the drying at 100° C. until constant weight



is attained. The weight of bismuth sulfide corresponds to not less than 37 nor more than 40 per cent bismuth.

**BISMUTH ETHYLCAMPHORATE.**— $C_{36}H_{57}BiO_{12}$ .—M. W. 890.8.—The bismuth III salt of *d*-camphoric acid monoethyl ester.

Bismuth ethylcamphorate occurs as a white amorphous solid, possessing a faint aromatic odor. It is insoluble in water but soluble in chloroform, ether, ethylene dichloride and vegetable oils. Its solubility in vegetable oils is increased by the addition of camphor. Bismuth ethylcamphorate softens at about 55° C. and melts in the range between 61 and 67 C.

Dissolve about 0.25 Gm. of bismuth ethylcamphorate in 25 cc. of ether in a separator; add diluted sulfuric acid sufficient to redissolve the white precipitate which forms at first; shake the mixture and then separate and wash the ether layer once with water: the aqueous acid layer responds to tests for bismuth. Extract the ether layer twice with 25 cc. portions of sodium hydroxide T.S., evaporate the combined alkaline extracts in a beaker to a volume of about 15 cc., cover the beaker with a watch glass and continue to heat for about two hours; filter, cool and acidify the solution with diluted sulfuric acid and allow the precipitate to crystallize. Separate and recrystallize the product from a small amount of hot water. The melting point of the dried *d*-camphoric acid obtained is from 186 to 188 C.

Place 0.25 Gm. of bismuth ethylcamphorate, accurately weighed, in a tared, low form weighing bottle; heat at 75-80° C. under pressure of 10 to 15 mm. of mercury to constant weight: the loss in weight is not more than 2.5 per cent.

Transfer about 0.5 Gm. of bismuth ethylcamphorate, accurately weighed, to a 500 cc. Kjeldahl flask, add 15 cc. of sulfuric acid and 15 cc. of nitric acid and boil gently until the mixture is colorless, adding more nitric acid if necessary. Continue to boil until the excess nitric acid is removed; cool and transfer the acid solution to a beaker, rinsing the flask with several 15 cc. portions of water. Dilute to about 100 cc. add two drops of methyl red T.S. and add diluted ammonia solution dropwise until the solution turns yellow. Add 2 cc. of nitric acid and dilute to about 150 cc. Heat to boiling, add five drops of 10 per cent ammonium phosphate solution and stir vigorously. Then add 40 cc. of the phosphate solution and digest the precipitate on a steam bath for 30 minutes, filter through a tared Gooch crucible and wash the precipitate with 3 per cent ammonium nitrate solution acidified with diluted nitric acid. Dry at 100° C. for 30 minutes and finally ignite to constant weight. The weight of the bismuth phosphate found corresponds to a bismuth content of not less than 21.5 per cent nor more than 23.5 per cent, calculated to the dried substance.

**BISMUTH SODIUM TARTRATE.**—A basic bismuth sodium tartrate containing 72.9 to 73.7 per cent of bismuth.

Bismuth sodium tartrate is a finely divided, white powder, odorless and tasteless; permanent in air. The product is soluble in about three parts of water, except for a slight residue (0.1 per cent); the residue is soluble in sodium hydroxide T.S. The aqueous solution is alkaline to litmus paper. When acid is added gradually to an aqueous solution of bismuth sodium tartrate a precipitate is produced, which dissolves on the gradual addition of an alkali.

Dissolve 0.5 Gm. of bismuth sodium tartrate in 25 cc. of water; heat to 50 C.; add 1.5 Gm. of sodium hydrosulfite dissolved in 5 cc. of 10 per cent diluted ammonia solution: a precipitate of metallic bismuth forms. To about 2 cc. of an aqueous solution (10 per cent) add a few drops of cupric sulfate T.S. A blue precipitate is formed, which is soluble in potassium hydroxide T.S. On standing, the alkaline solution gradually deposits a precipitate. Ignite 3 Gm. in a quartz crucible, cool, and cautiously add drop by drop just sufficient nitric acid to dissolve the residue when it is warmed; pour the acid solution into 100 cc. of water, evaporate the filtrate on the water bath to 30 cc., again filter and divide the filtrate into 5 cc. portions. To one portion add an equal

volume of diluted sulfuric acid: the liquid does not become cloudy (*lead*). Add an excess of diluted ammonia solution to another portion: the supernatant liquid does not exhibit a bluish tint (*copper*). Add to another portion diluted hydrochloric acid: a precipitate, insoluble in an excess of hydrochloric acid and soluble in diluted ammonia solution, is not formed (*silver*). Ignite 1 Gm. in a quartz crucible: the residue meets the requirements of the U. S. P. test for arsenic.

Dry about 1 Gm. of bismuth sodium tartrate, weighed accurately, at 100 C. to constant weight: the loss is from 2.6 to 3.6 per cent. Dissolve about 0.5 Gm. of bismuth sodium tartrate, accurately weighed, in 20 to 30 cc. of water and add sufficient hydrochloric acid to redissolve the precipitate first formed; saturate the solution with hydrogen sulfide; collect the precipitate of bismuth sulfide, wash it successively with water, alcohol, carbon disulfide, and ether and dry it at 100 C.: the weight of bismuth sulfide is equivalent to not less than 72.7 nor more than 73.9 per cent of bismuth (Bi).

**BISMUTH SODIUM THIOGLYCOLLATE.**— $C_6H_6BiNa_3O_6S_3$ .—M. W. 548.28.—A salt formed by the interaction of sodium thioglycollate and bismuth hydroxide. The product has the general formula  $Bi(SCH_2CO_2Na)_3$ , though it may differ slightly in composition from this formula. It contains approximately 38 per cent of bismuth.

Bismuth sodium thioglycollate occurs as a canary yellow, hygroscopic, noncrystalline, but granular substance possessing a garlic-like odor. It is freely soluble in water but the solutions are not stable.

Add 1 drop of diluted hydrochloric acid to 1 cc. of a 2 per cent solution of bismuth sodium thioglycollate solution: a heavy yellow precipitate separates that dissolves on the addition of another drop of acid. Add several drops of 36 per cent acetic acid to 1 cc. of a 2 per cent solution of bismuth sodium thioglycollate: no precipitate forms. Add 3 drops of diluted ammonia solution to 1 cc. of a 2 per cent solution: a slight change of color and a slight precipitate occurs within one-half hour. Add 1 drop of sodium hydroxide T.S. to 1 cc. of 2 per cent solution of bismuth sodium thioglycollate: a precipitate forms, insoluble in excess of reagent. Add several drops of cupric sulfate T.S. to 1 cc. of a 2 per cent solution of bismuth sodium thioglycollate: a precipitate forms that gives the suspension a murky greenish brown appearance. The precipitate dissolves in sodium hydroxide solution, leaving a yellow solution (*distinction from sodium or potassium bismuth tartrates*). Gently ignite an intimate mixture containing about 0.2 Gm. each of bismuth sodium thioglycollate and sodium carbonate, cool, add 3 cc. of water, add sufficient diluted hydrochloric acid to make the solution acid and boil: lead acetate paper held in the mouth of the test tube blackens.

Extract 0.2 Gm. of bismuth sodium thioglycollate with 10 cc. of chloroform or ether: no residue remains after the evaporation of the solvent (*free thioglycollic acid*). To 1 cc. of 2 per cent solution of bismuth sodium thioglycollate add sufficient diluted hydrochloric acid to just dissolve the precipitate first formed, and add several drops of barium chloride T.S.: a precipitate does not appear.

Heat an accurately weighed sample of bismuth sodium thioglycollate weighing about 1 Gm. in a 100° C. oven for one hour, cool in a desiccator, and weigh: the sample does not lose more than 5 per cent in weight. Transfer an accurately weighed sample of bismuth sodium thioglycollate weighing about 0.4 Gm. to an Erlenmeyer flask, dissolve in 100 cc. of water, add enough diluted hydrochloric acid just to dissolve the precipitate first formed and saturate with hydrogen sulfide until the bismuth is completely precipitated as bismuth sulfide. Collect the precipitate in a prepared Gooch crucible, wash with water, alcohol, ether, chloroform and ether in the order named, dry at 100° C., cool in a desiccator and weigh: the bismuth calculated from the bismuth sulfide is equivalent to not less than 37 per cent nor more than 39.5 per cent in the original calculated to the dry substance. Evaporate the filtrate from the bismuth determination to

a small bulk, transfer to a platinum dish, add sulfuric acid and evaporate to dryness; add a few drops of sulfuric acid, evaporate to dryness again, volatilize a small amount of ammonium carbonate from the dish, cool in a desiccator and weigh: the sodium calculated from the weight of sodium sulfate is not less than 12.23 per cent nor more than 13.04 per cent in the original substance calculated to the dry substance.

**BISMUTH SODIUM TRIGLYCOLLAMATE.**— $C_{24}H_{28}O_{25}N_4BiNa_7$ .—F. W. 1142.—A double salt of bismuthyl sodium triglycollamate and disodium triglycollamate containing approximately 18.3 per cent of bismuth.

Bismuth sodium triglycollamate occurs as a white, odorless, crystalline powder with a somewhat salty taste. It is stable on exposure to air and is unaffected by light. It is very soluble in water but insoluble in organic solvents such as acetone, ether and benzene. The pH of a 2 per cent aqueous solution is between 7 and 8.

Add a drop of diluted hydrochloric acid to 0.1 Gm. of bismuth sodium triglycollamate: no effervescence occurs (*carbonate*). One gram of bismuth sodium triglycollamate should show no more chloride than corresponds to 0.5 cc. of fiftieth-normal hydrochloric acid (*U. S. P. XIII*, p. 709).

Dissolve 2 Gm. of bismuth sodium triglycollamate in 15 cc. of distilled water, add 5 cc. of diluted hydrochloric acid, and shake the mixture until precipitation is complete. Collect the crystalline precipitate on a filter and use the filtrate for later tests. The melting point of the washed, dried crystals is not less than  $225^{\circ}C$ . Dissolve about 0.1 Gm. of the crystalline product, accurately weighed, in 50 cc. of hot water, add 2 drops of phenolphthalein T.S., and titrate with twentieth-normal sodium hydroxide. The neutralization equivalent should be not less than 94 nor more than 97.

Add 5 drops of barium chloride T.S. to 5 cc. of the filtrate: the solution shows no more sulfate than corresponds to 0.25 cc. of fiftieth-normal sulfuric acid.

To another 5 cc. portion of the filtrate add an equal amount of sulfuric acid (*caution!*) and cool the mixture. Superimpose ferrous sulfate T.S.: no brown ring is produced at the junction of the two liquids (*nitrate*).

Ignite 3 Gm. of bismuth sodium triglycollamate in a quartz crucible, not above  $700^{\circ}C$ ., cool and cautiously add, dropwise, just sufficient nitric acid to dissolve the residue when warmed. Pour the acid solution into 100 cc. of water, evaporate to 30 cc., filter and take three 5 cc. portions of the filtrate. To one portion add an equal amount of diluted sulfuric acid: the liquid does not become cloudy (*lead*). To the second portion add an excess of ammonia hydroxide: no bluish tint develops (*copper*). To the third portion add diluted hydrochloric acid: a precipitate, insoluble in excess hydrochloric acid and soluble in strong ammonia solution, is not formed (*silver*).

Mix 0.2 Gm. of bismuth sodium triglycollamate with 2 cc. of sulfuric acid. Heat the mixture until fumes of sulfur trioxide are evolved. Cool and dilute with water until the solution measures 5 cc. This solution meets the requirements of the test for arsenic (*U. S. P. XIII*, p. 618).

Dry about 1.2 Gm. of bismuth sodium triglycollamate, accurately weighed, at  $100^{\circ}C$ . for two hours: the loss in weight does not exceed 2 per cent.

Ignite about 1 Gm. of dried bismuth sodium triglycollamate, accurately weighed, in a shallow porcelain crucible in a muffle furnace at  $700^{\circ}C$ . Cool, dissolve the residue with 5 cc. of hydrochloric acid, and transfer the solution quantitatively to a 250 cc. beaker with 100 cc. of water, heat to boiling and saturate the solution with hydrogen sulfide. Collect the precipitate on a tared Jena or Gooch crucible, and wash successively with water, alcohol, ether, carbon disulfide, alcohol and ether. Dry the residue to constant weight at  $100^{\circ}C$ ., cool and weigh: the bismuth content calculated from the weight of bismuth sulfide obtained is not less than 18 per cent nor more than 19 per cent.

**BISMUTH TRIBROMOPHENATE.**—A basic bismuth tribromophenate of variable composition.

Bismuth tribromophenate is an amorphous, yellow powder, neutral to moistened litmus paper. It is only slightly soluble in water, alcohol, chloroform, liquid petrolatum, and vegetable oils. Alkalis and strong acid decompose it. It is stable at temperatures below 120 C.

Boil about 1 Gm. of the salt with 10 cc. of sodium hydroxide T.S., filter the liquid and acidify the filtrate with sulfuric acid: the white curdy precipitate produced, when washed and dried, melts from 90° to 95° C. (*tribromophenol*). The contents of the filter dissolve completely in diluted hydrochloric acid (*insoluble inert material*).

Boil 1 Gm. of bismuth tribromophenate with 20 cc. of a mixture of equal parts of 36 per cent acetic acid and water, cool the solution and filter. Free the filtrate from bismuth by saturating it with hydrogen sulfide, boil the mixture and again filter: the latter filtrate leaves not more than 0.005 Gm. of residue on evaporation and gentle ignition (*alkalis and alkaline earths*).

Shake 2 Gm. of bismuth tribromophenate, 20 cc. of ether, and 20 cc. of a mixture of equal volumes of hydrochloric acid and distilled water in a separatory funnel for one or two minutes. Draw off the aqueous portion and concentrate to about 4 cc.; pour it into 100 cc. of distilled water, filter, evaporate the filtrate on the water bath to 30 cc., again filter and divide this filtrate into portions of 5 cc. each. Mix one portion with an equal volume of diluted sulfuric acid: it does not become cloudy (*lead*). Treat another portion with a slight excess of diluted ammonia solution: the supernatant liquid does not exhibit a bluish tint (*copper*); another portion is not immediately affected by barium nitrate T.S. (*sulfate*).

Heat gently a mixture of about 0.2 Gm. of bismuth tribromophenate with 5 cc. of potassium hydroxide T.S. and about 0.2 Gm. of aluminum wire: the vapors evolved do not turn litmus blue (*nitrates*).

Shake 1 Gm. of bismuth tribromophenate frequently during 15 minutes with 30 cc. of alcohol, filter and rinse the flask with two separate 10 cc. portions of alcohol, allowing the washings to run through the filter. To the combined filtrate and washings add 5 cc. of tenth-normal sodium hydroxide, using a few drops of phenolphthalein T.S. as an indicator and determine the excess of alkali with tenth-normal hydrochloric acid: not more than 1 cc. of tenth-normal sodium hydroxide should be consumed by the alcoholic liquid (*free tribromophenol*).

Add 2 cc. of nitric acid to 2 Gm. of bismuth tribromophenate in a porcelain crucible, carefully evaporate to dryness on a sand bath and ash. Dissolve the residue in 5 cc. of concentrated hydrochloric acid and add to the solution 10 cc. of a saturated solution of stannous chloride in concentrated hydrochloric acid: the mixture should not darken on standing 30 minutes (*arsenic*).

Mix 0.5 Gm. of the salt with 10 cc. of a mixture of equal parts of hydrochloric acid and distilled water: no effervescence should occur (*carbonate*).

To about 0.5 Gm. of bismuth tribromophenate, accurately weighed, add 20 cc. of hydrochloric acid and digest on a water bath. Add 150 cc. of water and filter. Rinse the beaker with 30 cc. of acidulated water and allow the washings to run through the filter. Saturate the combined filtrate and washings with hydrogen sulfide (care being exercised that the solution is not too acid so as to prevent quantitative precipitation of the bismuth sulfide), filter off the bismuth sulfide, wash and dissolve in hot diluted nitric acid. Add a slight excess of diluted ammonia solution followed by 2 cc. of ammonium carbonate T.S. Allow to stand 30 minutes, filter off the precipitated bismuth hydroxide and heat to constant weight at dull red heat: the residue of bismuth oxide ( $\text{Bi}_2\text{O}_3$ ) should not be less than 45 per cent or more than 55 per cent of the original weight of bismuth tribromophenate taken, corresponding to not less than 40 per cent nor more than 49 per cent of bismuth.

**BRILLIANT GREEN.**— $C_{21}H_{29}N_2O_4S$ .—M. W. 482.54.—Tetraethyldiaminotriphenylcarbinol anhydride sulfate.

Brilliant green occurs as an olive-green crystalline powder, soluble in water (1 Gm. in 20 cc.) and soluble in alcohol (1 Gm. in 20 cc.). Brilliant green may be prepared by oxidation of the condensation product of benzaldehyde and diethylaniline. A solution of brilliant green in 50 per cent V/V aqueous alcohol possesses a characteristic adsorption curve with a maximum at 6,280 Å.

Dissolve 0.1 Gm. of brilliant green in 50 cc. of water. To one 10 cc. portion of this solution add a few drops of diluted hydrochloric acid: the color changes from an olive-green to yellow. To another 10 cc. portion add several drops of sodium hydroxide T.S.: a brown to violet-brown precipitate forms. To another 10 cc. portion add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride T.S.: a white precipitate results.

Dry an accurately weighed portion of brilliant green to constant weight at 110 C.: the loss in weight does not exceed 7.5 per cent. Ignite an accurately weighed specimen of brilliant green to constant weight: the residue is not more than 1 per cent.

Brilliant green meets the requirement limit for lead given under Methylrosanilin Chloride, U. S. P. XIII.

Dissolve 0.3 Gm. of brilliant green, accurately weighed, in 150 cc. of diluted alcohol and proceed as directed under "Assay," *National Formulary* VIII, p. 649: the amount of brilliant green found corresponds to not less than 95.0 per cent nor more than 101 per cent of the dried substance.

**BROMISOVALUM.**— $C_8H_{11}BrN_2O_2$ .—M. W. 223.08.—2-Monobromoisovalerylurea, obtained by the interaction of urea with bromoisovaleryl bromide.

Bromvalerylurea forms small, white, almost tasteless needles which are easily soluble in hot water, ether, alcohol and alkalis, but less readily soluble in cold water. It sublimes on heating and melts from 147° to 149° C.

Bromvalerylurea can be precipitated from a 10 per cent sodium hydroxide solution with acids. The presence of bromine may be demonstrated by fusion with sodium carbonate and potassium nitrate and testing for bromide with silver nitrate T.S. On heating an alcoholic solution of bromvalerylurea with sodium ethylate for several hours on the water bath, sodium bromide will precipitate. If this is filtered off and the filtrate evaporated, a crystalline mass remains which can be recrystallized from water. This is dimethylacrylic acid, melting at 280° C. If 1 Gm. of bromvalerylurea is boiled for about one minute with 10 per cent solution of sodium hydroxide, ammonia obtained from the urea will be given off. If the hot liquid is then cooled, acidified with nitric acid and extracted with ether, and the ether evaporated, an oily fluid, 1-bromoisovaleric acid, which has the specific odor of valeric acid, will remain. The biuret reaction cannot be obtained. On melting bromvalerylurea and adding concentrated sodium hydroxide solution and cupric sulfate T.S. no color reaction will take place.

**BURBOT LIVER OIL.**—The oil extracted from the livers of the Burbot (*Lota maculosa*), family Gadidae. It is biologically assayed to have a potency of not less than 4,480 units of vitamin A (U. S. P.) per gram and of not less than 640 units of vitamin D (U. S. P.) per gram.

Burbot liver oil is a pale, yellow, oily liquid. It has a slightly fishy but not rancid odor and a fishy taste. It is slightly soluble in alcohol but is soluble in ether, chloroform, benzene, carbon disulfide and ethyl acetate. The specific gravity is from 0.921 to 0.927 at 25 C. The refractive index is from 1.479 to 1.482 at 20° C.

A solution of one drop of the oil in 1 cc. of chloroform, when shaken with one drop of sulfuric acid, acquires a light violet color, changing to violet, dark green and finally brown. Treat 5 cc. of oil with 5 cc.

of benzene and centrifuge for 25 minutes at 25° C.: no precipitate forms and a clear solution remains.

Fill a tall cylindric, standard oil-sample bottle of about 120 cc. capacity with burbot liver oil at a temperature between 23 and 28 C., stopper, and immerse the bottle in a mixture of ice and distilled water for five hours: the oil remains fluid and forms no deposit.

Dissolve 2 Gm. of burbot liver oil, accurately weighed, in 20 cc. of a mixture of equal volumes of alcohol and ether, which previously has been neutralized with tenth-normal sodium hydroxide, using five drops of phenolphthalein T. S. as indicator, and titrate with tenth-normal sodium hydroxide to the production of a pink color which persists for fifteen seconds: not more than 1 cc. of tenth-normal sodium hydroxide is required (*free acid*). The amount of unsaponifiable matter as determined by the method of U. S. P. XIII, p. 648, is not less than 0.9 per cent nor more than 3.0 per cent. The saponification value as determined by the method of U. S. P. XIII, p. 647, is not less than 184 nor more than 196. The iodine value as determined by the method of U. S. P. XIII, p. 647, on 0.18 to 0.20 Gm. of sample, accurately weighed, is not less than 155 nor more than 180.

**BUTABARBITAL SODIUM.**— $C_{10}H_{15}N_2O_3Na$ .—M. W. 234.23.—Sodium 5-ethyl-5(1-methyl propyl) barbiturate.

Butabarbital sodium occurs as a white, bitter-tasting powder. It is soluble in water (1 in 2) and in alcohol (1 in 6.7); practically insoluble in dry ether and in benzene. The pH of a 1 per cent solution is from 9.0 to 10.2.

Dissolve about 0.5 Gm. of butabarbital sodium in 100 cc. of water and acidify the solution with diluted hydrochloric acid. Allow the ethyl *sec*-butyl barbituric acid to crystallize from solution, collect it on a filter, wash with water and dry at 100° C.: the crystals melt at 165–168° C.

Incinerate about 0.1 Gm. of butabarbital sodium: the residue responds to tests for sodium carbonate. Dissolve about 0.3 Gm. of butabarbital sodium in 10 cc. of water and divide into two portions. To one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in an excess of strong ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in an excess of strong ammonia solution.

Dissolve about 0.5 Gm. of butabarbital sodium in 5 cc. of sulfuric acid: no more color is produced than that of matching fluid A (U. S. P.) Dissolve about 0.25 Gm. of butabarbital sodium in 25 cc. of water. Add 5 cc. of diluted nitric acid, allow to stand ten minutes and filter. Separate 10 cc. portions of the filtrate yield no greater opalescence on addition of 0.5 cc. of silver nitrate T.S. than that produced by 0.25 cc. of tenth-normal hydrochloric acid in 50 cc. of water (*chloride*) and no turbidity on addition of 1.0 cc. of barium chloride T.S. (*sulfate*).

Dissolve 2.0 Gm. of butabarbital sodium in 42 cc. of water and add slowly, with stirring, 8 cc. of normal hydrochloric acid. Filter, rejecting the first 5 cc. of the filtrate: 25 cc. of the filtrate shows no more heavy metals than 30 parts per million (U. S. P.).

Shake 0.5 Gm. of butabarbital sodium with 20 cc. of anhydrous ether for ten minutes, decant the ether through a filter, evaporate the ether in a tared dish, and dry the residue at 100° C.: the weight of the residue does not exceed 3 mg. (*uncombined butabarbital*).

Dry about 1.0 Gm. of butabarbital sodium, accurately weighed, at 100° C. for 20 hours: the loss in weight is not more than 5 per cent.

Dissolve about 0.5 Gm. of butabarbital sodium, accurately weighed, in 10 cc. of water in a separatory funnel; add to the solution 15 cc. of diluted hydrochloric acid; and extract the liberated butabarbital with eight successive portions of ether, using 25 cc., 20 cc., 20 cc., 10 cc., 10 cc., 10 cc., 10 cc. and 10 cc., respectively. Wash the combined ether extracts with two 5 cc. portions of distilled water. Evaporate the washed ether extract in a tared dish or beaker at a low temperature in a stream of warm air, and dry the residue at 100° C. for two hours: the weight of the residue corresponds to not less than 89 per cent or more than 91 per cent of the sample taken, calculated on the moisture-free basis.

**BUTALLYLONAL.**— $C_{11}H_{15}BrN_2O_3$ .—M. W. 303.16.—5-*sec.* butyl-5- $\beta$ -bromoallyl barbituric acid.

Butallylonal occurs as a fine, white, crystalline powder, with a slightly bitter taste. It is completely soluble in alcohol and ether, very slightly soluble in cold water; and insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Butallylonal melts at 130° to 133° C.

Place approximately 1 Gm. of butallylonal in a 25 cc. glass stoppered cylinder, add 10 cc. of water and 1 cc. of sodium hydroxide T.S. and shake for one minute, filter through paper and divide into two portions; to one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in 10 cc. of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in 5 cc. of diluted ammonia solution.

Fuse about 0.1 Gm. of butallylonal and 1 Gm. of crushed potassium hydroxide, previously moistened with 1 cc. of alcoholic potassium hydroxide solution, in a nickel crucible; it is decomposed with the evolution of ammonia; cool, dissolve the residue in 10 cc. of water, add 10 cc. of diluted nitric acid, filter through paper; to the filtrate add 5 cc. of silver nitrate T.S.: a curdy dirty white precipitate results, soluble in excess of strong ammonia solution.

Dissolve 0.1 Gm. of butallylonal in 1 cc. of sulfuric acid: the liquid assumes a yellow color, changing slowly to a brownish red, finally to a dark red. Place 1 Gm. of butallylonal in a 25 cc. glass stoppered cylinder, add 10 cc. of water, shake for one minute, filter through paper and divide into two portions. To one portion add 0.5 cc. of bromine T.S.: an immediate discoloration occurs. To the other portion add 0.1 cc. of tenth-normal potassium permanganate: a yellow color appears immediately.

Boil 0.5 Gm. of butallylonal with 50 cc. of water for two minutes: no odor develops; cool and filter; separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate T.S. (*sulfate*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Ignite about 1 Gm. of butallylonal, accurately weighed: the residue does not exceed 0.1 per cent. Do a Carius determination on about 0.25 Gm. of butallylonal, accurately weighed: the bromine found should be not less than 26.1 per cent nor more than 26.6 per cent. Dissolve about 0.5 Gm. of butallylonal, accurately weighed, in 25 cc. of previously neutralized alcohol; dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide, using thymolphthalein T.S. as an indicator; the amount of tenth-normal sodium hydroxide consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of *sec.*-butylbromoallyl barbituric acid.

**BUTALLYLONAL SODIUM.**— $C_{11}H_{14}BrN_2NaO_3$ .—M. W. 325.15.—The monosodium salt of 5-*sec.* butyl-5- $\beta$ -bromoallyl barbituric acid.

Butallylonal sodium occurs as a fine, white, crystalline powder, possessing a bitter taste. It is soluble in water and alcohol and slightly soluble in ether and chloroform. A 10 per cent aqueous solution is alkaline to litmus and phenolphthalein and has a pH of approximately 9.5.

Transfer 5 cc. of a 10 per cent solution of butallylonal sodium to a test tube, add 2 cc. of diluted hydrochloric acid; allow the precipitate to crystallize, filter, wash and recrystallize from an ethanol-water mixture: the melting point of the butallylonal is from 130° to 133° C.

Transfer 5 cc. portions of a 10 per cent solution of butallylonal sodium to two test tubes and to one add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in 10 cc. of strong ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in 5 cc. of strong ammonia solution.

Dissolve 0.1 Gm. of butallylonal sodium in 1 cc. of sulfuric acid: the liquid assumes a yellow color, changing to brownish red and finally to dark red. Acidify 40 cc. of a 10 per cent solution of butallylonal sodium

with diluted nitric acid and filter; separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of silver nitrate T.S. (*chloride*); no turbidity with 1 cc. of barium nitrate T.S. (*sulfate*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Transfer about 0.5 Gm. of butallylinal sodium, previously dried and accurately weighed, to a tared porcelain dish and add 2 cc. of sulfuric acid; evaporate the excess acid, ash the residue and ignite at 900° C.: the weight of sodium sulfate is not less than 21.4 per cent nor more than 22.2 per cent. Run a Carius determination on about 0.3 Gm. of butallylinal sodium, dried and accurately weighed: the bromine found is not less than 24.3 per cent nor more than 24.8 per cent. Transfer a sample of butallylinal sodium, dried and accurately weighed, to a Kjeldahl flask and digest with sulfuric acid in the presence of selenium, dilute, make alkaline, distill into standard acid and titrate the excess acid with standard alkali: the nitrogen content is not less than 8.3 per cent nor more than 8.8 per cent.

**BUTAMBEN PICRATE.** —  $C_{28}H_{33}N_5O_{11}$ . — F. W. 615.59.—A compound consisting of one molecule of trinitrophenol (picric acid) and two molecules of the normal butyl ester of 4-aminobenzoic acid.

Butamben picrate is a yellow, odorless, amorphous powder, with a slightly bitter taste. One part of butamben picrate is soluble in 2,000 parts of water, and in 100 parts of cottonseed oil; it is soluble in alcohol, chloroform, ether and benzene. It melts at 109° to 110° C.

The aqueous solution of butamben picrate is greenish yellow; the color is intensified by the addition of alkali and is decreased by acid. A saturated aqueous solution of butamben picrate is not affected by the addition of mercuric potassium iodide T.S., of silver nitrate T.S. or of hydrogen sulfide solution. A few drops of saturated solution of sodium nitrite added to the acidulated solution of butamben picrate and followed by a few drops of a slightly alkaline solution of betanaphthol produces a salmon-colored precipitate which quickly darkens. A purplish-red color is produced if a 1 per cent potassium cyanide solution be added to an aqueous solution of butamben picrate.

Incinerate 0.5 Gm. of butamben picrate, accurately weighed: the ash does not exceed 0.1 per cent.

**BUTETHAL.**— $C_{10}H_{16}N_2O_3$ .—M. W. 212.24.—5-*n*-Butyl-5-ethylbarbituric acid.

Butethal occurs as a white, crystalline, odorless powder, with a slightly bitter taste. It is readily soluble in alcohol, about 1 in 5, and ether, about 1 in 10; very slightly soluble in cold water; and insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Butethal melts at 124-127° C. It is stable in air.

Place 0.3 Gm. in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. sodium hydroxide T.S. and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions. To one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in 10 cc. of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in 5 cc. of diluted ammonia solution. Boil 0.5 Gm. with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia.

Dissolve 0.1 Gm. in 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Boil 0.5 Gm. with 50 cc. water for two minutes: no odor develops; cool and filter: separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*chloride*), and no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate T.S. (*sulfate*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Ignite about 1 Gm., accurately weighed: the residue does not exceed 0.1 per cent.

Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously



neutralized alcohol, dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide, using thymolphthalein T.S. as an indicator: the amount of tenth-normal sodium hydroxide consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of butylethyl barbituric acid.

**BUTETHAMINE FORMATE.—Monocaine Formate-Novocol.**— $C_{14}H_{22}N_2O_4$ .—M. W. 282.34.—2-Isobutylamino ethyl *p*-aminobenzoate formate.—2-*p*-Aminobenzoxy-N-isobutyl ethylamine formate.

Monocaine Formate occurs as odorless, white crystals, which melt at 136-139° C. It is freely soluble in water and in alcohol, very slightly soluble in benzene, and slightly soluble in chloroform and in ether. The *pH* of a 1 per cent aqueous solution is about 6.1.

Extract about 0.15 Gm. of Monocaine Formate as described in the assay given later. Evaporate the aqueous layer to dryness on a steam bath. Dissolve the residue in 1 cc. of four-normal hydrochloric acid; add 40 mg. of *o*-phenylenediamine and reflux the solution gently for 45 minutes. Allow the solution to cool, neutralize with strong ammonia solution and let stand for a few hours to allow crystal formation to occur. Filter the crystals from the mother liquor and recrystallize from water. The benzimidazole derivative formed from the formic acid present melts at 171 C.

Evaporate the chloroform layer from the foregoing extraction to dryness at a temperature of about 60 C. in a stream of air. Dissolve the residue in 5.5 cc. of tenth-normal hydrochloric acid. Dilute one half of the acid solution to 40 cc. and carry out the following identification tests: Add to a 5 cc. portion of the diluted solution 0.5 cc. of diluted hydrochloric acid and 0.5 cc. of 10 per cent sodium nitrite solution, followed by 10 cc. of diluted ammonia solution containing 0.2 Gm. of beta-naphthol: an orange precipitate forms which is soluble in ether. Add 1 cc. of mercuric potassium iodide T.S. to 2 cc. of the diluted solution: a white precipitate forms. Dilute the second half of the acid solution to 5 cc. with water. Add two drops of sulfuric acid and 1 cc. of a saturated solution of sodium nitrite; heat to 50 C.: a yellow emulsion forms. Continue heating: an orange-red solution results and reddish oil droplets form on the bottom of the tube and in the froth.

Accurately weigh about 0.2 Gm. of Monocaine Formate. Dry over phosphorus pentoxide in a vacuum desiccator: the loss in weight is not more than 0.5 per cent. Ash about 0.2 Gm. of Monocaine Formate, accurately weighed: the ash content is not more than 0.15 per cent.

Transfer 0.15 Gm. of Monocaine Formate, accurately weighed, to a separatory funnel containing 25 cc. of chloroform. Add 10 cc. of water to dissolve the crystals; then add three drops of strong ammonia solution and extract the aqueous solution with the chloroform. Drain the chloroform layer through a pledget of cotton. Repeat the extraction four more times with 15, 10, 10 and 10 cc. portions of chloroform. Evaporate the combined chloroform extracts at a temperature of about 60 C. in a stream of air. Dissolve the residue in 5 cc. of neutral alcohol and heat to insure complete solution. Add 10 cc. of tenth-normal hydrochloric acid and two drops of methyl red T.S. indicator. Rinse the sides of the beaker with about 10 cc. of water and titrate the excess acid with tenth-normal sodium hydroxide. Each cc. of tenth-normal hydrochloric acid is equivalent to 0.02823 Gm. of Monocaine Formate: the amount of Monocaine Formate found is not less than 95.0 per cent.

Decant the residual aqueous layer in the separatory funnel into a 250 cc. beaker. Wash the funnel with two 20 cc. portions of water and add the washings to the original solution. To the combined mixture add 1 Gm. of sodium carbonate and dilute the solution with water to approximately 100 cc. Evaporate the solution to about 50 cc. by gentle boiling. Titrate 25 cc. of tenth-normal potassium permanganate into the hot solution. Carefully acidify (*caution*) the solution with concentrated sulfuric acid. Clear the solution by titration with 15 cc. of tenth-normal oxalic acid and finally titrate the excess oxalic acid with more of the tenth-normal potassium permanganate. The difference between the total volumes of potassium permanganate and oxalic acid is due to the oxidation of formic acid. One

cc. of tenth-normal potassium permanganate is equivalent to 0.002301 Gm. of formic acid: the amount of formic acid found is not less than 15.8 per cent nor more than 16.8 per cent of the weight taken.

**BUTETHAMINE HYDROCHLORIDE.**—Monocaine Hydrochloride-Novocol.— $C_{13}H_{20}N_2.HCl$ .—M. W. 272.78.—2-Isobutylamino ethyl *p*-aminobenzoate hydrochloride.—2-*p*-Aminobenzoxo-N-isobutyl ethylamine hydrochloride.

Monocaine hydrochloride occurs as a white, odorless, crystalline powder possessing a bitter taste and having anesthetizing effects. It melts within the range 192-196° C. It is sparingly soluble in water, slightly soluble in alcohol and chloroform, very slightly soluble in benzene and practically insoluble in ether. The *pH* of a 1 per cent aqueous solution is about 4.7.

Dissolve 0.1 Gm. of Monocaine Hydrochloride in 50 cc. of water. Add 1 cc. of silver nitrate T.S. to a 5 cc. portion of the solution: a white precipitate forms, which is soluble in strong ammonia solution. To another 5 cc. portion of the solution add 0.5 cc. of diluted hydrochloric acid and 0.5 cc. of 10 per cent sodium nitrite solution, followed by 10 cc. of diluted ammonia solution containing 0.2 Gm. of beta-naphthol: an orange precipitate forms which is soluble in ether. Add 1 cc. of mercuric potassium iodide T.S. to 2 cc. of the Monocaine Hydrochloride solution: a white precipitate forms.

Dissolve 0.1 Gm. of Monocaine Hydrochloride in 5 cc. of water. Add two drops of sulfuric acid and 1 cc. of a saturated solution of sodium nitrite; heat to 50° C.: a yellow emulsion forms. Continue heating: an orange-red solution results, and reddish oil droplets form on the bottom of the tube and in the froth.

Weigh accurately about 0.5 Gm. of Monocaine Hydrochloride. Dry at 110 C. to constant weight: the loss in weight is less than 0.5 per cent. Ash the dried sample: the weight of the residue is not more than 0.25 per cent.

Dissolve about 0.25 Gm. of Monocaine Hydrochloride, accurately weighed, in 100 cc. of water; add 1 cc. of nitric acid and 20 cc. of silver nitrate solution; digest, filter, wash, dry at 110 C. and weigh the precipitate: the chlorine content is not less than 12.8 per cent nor more than 13.2 per cent.

Transfer about 0.15 Gm. of Monocaine Hydrochloride, accurately weighed, to a separatory funnel and proceed according to the method described for procaine hydrochloride in the book *Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, p. 667, Method II. Each cubic centimeter of tenth-normal hydrochloric acid is equivalent to 0.02728 Gm. of Monocaine Hydrochloride: the Monocaine Hydrochloride content is not less than 95 per cent nor more than 105 per cent.

**BUTYLCHLORAL HYDRATE.**— $C_4H_7Cl_3O_2$ .—M. W. 193.47.—Trichlorobutylidene Glycol.—Croton Chloral Hydrate.—2,2,3-Trichlorobutane-1,1-diol.

Butylchloral hydrate occurs in pearly white, orthorhombic laminae, having a pungent but not an acrid odor, and an acrid, nauseous taste. It fuses at about 78° C. to a transparent liquid, which, on cooling, begins to solidify at about 71 C. It is soluble in about 50 parts of water, and in its own weight of glycerin or of alcohol (90 per cent); it slowly dissolves in 20 parts of chloroform. From a solution in alcohol, it is precipitated by the gradual addition of water in the form of globules said to consist of butylchloral alcoholate,  $C_4H_5Cl_3O$ .  $C_2H_5OH$ . The alcoholic solution is neutral, and the aqueous solution is neutral or but slightly acid to litmus.

It gives no precipitate with silver nitrate T.S. Heat about 0.2 Gm. of butylchloral hydrate with 10 cc. of sodium hydroxide T.S. and add 2 drops of a saturated aqueous solution of aniline: the odor of phenyl isocyanide cannot be detected (*chloral hydrate*).

**CARBETHYL SALICYLATE.**— $C_{19}H_{18}O_7$ .—M. W. 358.33.—The carbonic acid ester of ethyl salicylate.

Carbethyl salicylate occurs as white, odorless and tasteless crystals. It is almost insoluble in water and diluted hydrochloric acid. It is slightly soluble in ether and alcohol but readily soluble in chloroform and acetone. It melts between 96 and 99 C.

Transfer about 2 Gm. of carbethyl salicylate to a test tube, add 5 cc. of half normal alcoholic potassium hydroxide and heat on the steam bath for five minutes: the product dissolves, and the formation of a precipitate follows; cool, decant the supernatant liquid, add 6 per cent acetic acid to the precipitate; it effervesces; add an equal volume of water to the decanted liquid: a colorless oil separates, having the odor of ethyl salicylate. Transfer about 1 Gm. of carbethyl salicylate to an Erlenmeyer flask, add 20 cc. of normal sodium hydroxide and 20 cc. of alcohol and boil under a reflux condenser for 30 minutes; cool, and acidify the solution by addition of diluted sulfuric acid; extract the solution with 20 cc. of ether, filter the ether and evaporate to dryness: the residue responds to qualitative tests for salicylic acid.

Dissolve about 0.5 Gm. of carbethyl salicylate in 10 cc. of sulfuric acid: the solution remains colorless for five minutes (*readily carbonisable substances*). Transfer about 0.5 Gm. of carbethyl salicylate to a test tube, add 10 cc. of water and a few drops of ferric chloride T.S.: no blue color develops (*salicylic acid*).

Transfer about 1 Gm. of carbethyl salicylate, accurately weighed, to a tared weighing bottle; heat in an oven at 100° C. for one hour; cool in a desiccator and weigh: the loss in weight is not greater than 1 per cent. Transfer about 0.5 Gm. of carbethyl salicylate, accurately weighed, to a platinum dish and ignite: the ash is not more than 0.2 per cent.

Transfer about 1 Gm. of carbethyl salicylate, accurately weighed, to an Erlenmeyer flask, add 40 cc. of half-normal alcoholic potassium hydroxide, boil under a reflux condenser on the steam bath for three hours, wash the condenser and add the washings to the flask; remove the alcohol by evaporating to about one-third the volume, adding 50 cc. of water and evaporating to about 15 cc. Transfer the solution to a 250 cc. volumetric flask and make up to volume by addition of water. Transfer a 25 cc. aliquot to an Erlenmeyer flask and test the solution according to the method for total salicylate described in the *Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, page 674, Iodine Method, paragraph 27: the weight of the tetraiodophenylene quinone multiplied by 0.5208 and by the aliquot factor is equivalent to not less than 98.5 per cent nor more than 100.5 per cent of the sample taken.

**CETYL PYRIDINIUM CHLORIDE.**— $C_{21}H_{40}ClNO$ .—M. W. 357.99.—The monohydrate of the quaternary salt of pyridine and cetyl chloride.

Cetyl pyridinium chloride occurs as a white powder possessing a slight odor. It melts within the range 77-83° C. It is very soluble in water, alcohol and chloroform, and only very slightly soluble in benzene and in ether. The pH of a 1 per cent aqueous solution is 6.0 to 7.0, as determined by the use of indicators (glass electrode instruments give variable results). The surface tension at 25° C. of a 0.1 per cent aqueous solution is about 43.00; of a 1.0 per cent aqueous solution, about 41.40; and of a 10 per cent aqueous solution, about 38.15.

Dissolve 0.1 Gm. of cetyl pyridinium chloride in 50 cc. of water. Add 1 cc. of silver nitrate solution to a 5 cc. portion of the solution: a white precipitate forms, which is soluble in strong ammonia solution.

Add 5 cc. of about one hundredth molar potassium ferricyanide to 5 cc. of the cetyl pyridinium chloride solution: a yellow precipitate forms. Add 1 cc. of a saturated potassium thiocyanate solution to a 1 cc. portion of the cetyl pyridinium chloride solution: a white gelatinous precipitate forms. Add 1 cc. of saturated picric acid solution to 1 cc. of the cetyl pyridinium chloride solution: a yellow precipitate forms.

Heat gently about 0.25 Gm. of cetyl pyridinium chloride contained

in a test tube until the substance melts and a brown color develops: the odor of pyridine is readily detected.

Weigh, accurately, about 0.5 Gm. of cetyl pyridinium chloride. Dry to constant weight in a vacuum over phosphorous pentoxide: the loss in weight is not less than 4.5 per cent nor more than 5.5 per cent. Ash the dried sample: the weight of the residue is not more than 0.2 per cent.

Weigh, accurately, about 0.25 Gm. of cetyl pyridinium chloride. Transfer to a 100 cc. volumetric flask. Add 5 cc. of buffer solution (260 Gm. of sodium acetate and 250 cc. of 36 per cent acetic acid, mixed with water to make 1 liter). Add 50 cc. of one hundredth molar potassium ferricyanide. Dilute to the mark with water, mix, allow to stand one hour and filter, discarding the first 15 cc. of the filtrate. Add 5 cc. of 10 per cent potassium iodide solution to a 50 cc. aliquot of the filtrate in an iodine flask. Add 10 cc. of concentrated hydrochloric acid and allow to stand for one minute. Add 10 cc. of 10 per cent zinc sulfate solution and titrate with one hundredth normal sodium thiosulfate, using starch T.S. near the end of the titration. Each cc. of one hundredth normal sodium thiosulfate is equivalent to 0.01074 Gm. of cetyl pyridinium chloride monohydrate: the cetyl pyridinium chloride monohydrate content is not less than 97 per cent nor more than 103 per cent.

**CHLORGUANIDE HYDROCHLORIDE.**— $C_{11}H_{16}N_5 \cdot Cl \cdot HCl$ .—M. W. 290.2. —  $N^1$ -(p-chlorophenyl)- $N^5$ -isopropylbiguanide hydrochloride.

Chlorguanide hydrochloride occurs as odorless, colorless, fine crystals, or as a crystalline powder, possessing a bitter taste. It is soluble in alcohol, slightly soluble in water and practically insoluble in chloroform and in ether. The pH of a filtered, saturated solution is between 5.8 and 6.3. Chlorguanide hydrochloride melts between 248° and 252° C. It exhibits an ultraviolet absorption maximum at 2590 Å., when dissolved in alcohol ( $E \frac{1\%}{1 \text{ cm.}} = 690 \pm 7$ ).

Prepare 50 cc. of a saturated solution of chlorguanide hydrochloride in water and divide into five portions in separate test tubes. To one portion add 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S.: a white precipitate forms. To another portion add 5 drops of iodine T.S.: an orange-brown precipitate forms. To another portion add 5 drops of potassium ferrocyanide T.S., rendered slightly acid to litmus with diluted nitric acid: a white precipitate forms which is soluble on addition of a few drops of diluted nitric acid. To another portion add 5 drops of a slightly acid solution of potassium dichromate T.S.: a yellow precipitate forms which is soluble in a few drops of diluted nitric acid. To another portion add bromine T.S., dropwise: a yellow precipitate forms which immediately redissolves on mixing; on addition of an excess of bromine T.S., a permanent orange precipitate forms.

Dissolve about 0.1 Gm. of chlorguanide hydrochloride in 25 cc. of water in a separatory funnel and add 10 cc. of tenth-normal sodium hydroxide. Extract the precipitated chlorguanide base with 25 cc. of ether. Separate, filter the ether extract, evaporate to near dryness, and dry the residue at 100° C.: the residue melts between 130° and 135° C.

Dry about 1 Gm. of chlorguanide hydrochloride, accurately weighed, at 100° C. for three hours: the loss in weight is not more than 0.3 per cent. Ash about 0.5 Gm. of chlorguanide hydrochloride, accurately weighed, in the presence of sulfuric acid: the residue is not more than 0.1 per cent.

Transfer about 0.2 Gm. of chlorguanide hydrochloride to an Erlenmeyer flask, add 50 cc. of water and dissolve the solid. Add 1 cc. of nitric acid and exactly 40 cc. of fiftieth-normal silver nitrate. Add 3-5 cc. of nitrobenzene and swirl the flask to entrap the precipitated silver chloride. Add 3 cc. of ferric ammonium sulfate T.S., and titrate with fiftieth-normal ammonium thiocyanate. Each cc. of fiftieth-normal silver nitrate is equivalent to 0.709 mg. of chlorine. The readily ionizable chlorine content is not less than 11.5 per cent nor more than 12.3 per cent, calculated to the dry substance.

Determine the nitrogen content of chlorguanide hydrochloride by the Kjeldahl method: the nitrogen content is not less than 23.5 per cent nor more than 24.5 per cent, calculated to the dry substance.

Transfer about 0.2 Gm. of chlorguanide hydrochloride to a separatory funnel, add 25 cc. of water and 10 cc. of sodium hydroxide T.S. Extract the precipitated chlorguanide base with successive 30 cc., 25 cc., 10 cc., 10 cc., and 10 cc. portions of ether. Combine the ether extracts, wash with 10 cc. of water, and filter the ether solution through a cotton pledget. Evaporate the combined ether extracts in a tared beaker using a stream of warm air. Dry the residue at 100° C. for one hour: the weight of the residue is not less than 85.7 per cent nor more than 89.2 per cent, calculated to the dry substance.

**CHLOROQUINE DIPHOSPHATE.** —  $C_{18}H_{32}ClN_3O_8P_2$ . — M. W. 515.88. — 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline diphosphate.

Chloroquine diphosphate occurs as a white, crystalline powder, possessing a bitter taste. It melts in the range 193-195° C. Two modifications of chloroquine diphosphate are obtainable. The second form melts at 215-218° C. It is freely soluble in water; and practically insoluble in alcohol, benzene, chloroform, and ether. The pH of a 1 per cent solution is about 4.5.

Dissolve about 50 mg. of chloroquine diphosphate in 3 cc. of water. Add a few drops of ammonium molybdate T.S.: a white precipitate develops immediately.

Dissolve 20 mg. of chloroquine diphosphate in 20 cc. of water. Add 5 cc. of a saturated aqueous solution of picric acid: a yellow precipitate forms immediately. Filter off the precipitate, wash with water and air-dry on the filter funnel: the product melts from 205-210° C. (*Caution!*).

Dissolve 0.25 Gm. of chloroquine diphosphate in 50 cc. of water. Add 1 cc. of strong ammonia solution and extract with two 30 cc. portions of cyclohexane. Evaporate the cyclohexane solution to dryness on the steam bath. Place the residual oil in a vacuum desiccator over phosphorus pentoxide and allow to stand over night to permit crystallization: the solid material melts at a temperature of 87-90° C.

Dry about 0.25 Gm. of chloroquine diphosphate, accurately weighed, in vacuum over phosphorus pentoxide at room temperature for 48 hours: the loss in weight does not exceed 2.0 per cent.

Dissolve about 0.2 Gm. of chloroquine diphosphate, accurately weighed, in 50 cc. of water. Dissolve 1.5 Gm. of bismuth oxynitrate in 10 cc. of nitric acid and dilute to 100 cc. with water. Add 50 cc. of the bismuth solution to the solution of chloroquine diphosphate. Digest for two hours on the steam bath, filter into a tared Gooch crucible and wash with dilute nitric acid (2 cc. to 100 cc.). Wash successively with 20 cc. portions of water, alcohol, and ether. Dry in an oven at 100° C. for two hours: the phosphorus content is not less than 11.80 per cent nor more than 12.25 per cent.

Weigh, accurately, about 0.2 Gm. of chloroquine diphosphate. Dissolve in 50 cc. of water and transfer to a separatory funnel. Add 5 cc. of strong ammonia solution and extract with 25, 20, 15, 10 and 10 cc. portions of ether. Drain the combined ether extracts through a cotton pledget into a 100 cc. tared beaker. Evaporate the solution on the steam bath to dryness and finally heat at 100° C. for 30 minutes: the residue, calculated to chloroquine diphosphate, is not less than 98 per cent nor more than 102 per cent.

**CHOLINE DIHYDROGEN CITRATE.** —  $C_{11}H_{21}NO_8$ . — M. W. 295.29. — Trimethyl hydroxyethyl ammonium citrate. — The dihydrogen citrate of trimethyl ethanolammonium hydroxide.

Choline dihydrogen citrate occurs as a white, crystalline, granular substance, possessing an acid taste. It melts at 105-107.5° C. It is freely soluble in water; very slightly soluble in alcohol; and practically

insoluble in benzene, in chloroform, and in ether. The pH of a 25 per cent solution is about 4.25.

Add 1 cc. of a 1 per cent solution of the choline salt to 2 cc. of cobaltous chloride solution (U. S. P. test solution diluted 1 to 25). Add 2 cc. of 2 per cent potassium ferrocyanide solution: an emerald-green color develops immediately.

Add 0.2 cc. of mercuric sulfate T.S. to 2 cc. of a 10 per cent solution of choline dihydrogen citrate. Heat the mixture to boiling and then add 5 drops of potassium permanganate T.S.: a precipitate develops with a slight yellow color.

Dissolve 0.5 Gm. of choline dihydrogen citrate in 2 cc. of water. Add the choline solution to 3 cc. of a saturated picric acid solution. Allow the aqueous solution to slowly evaporate. Filter off the crystalline material and wash thoroughly with ether: the crystals melt from 245-251° C. (*Caution!*) with considerable decomposition.

Dissolve 0.5 Gm. of choline dihydrogen citrate in 2 cc. of water. Add to 1 cc. of the choline solution a few drops of phosphotungstic acid T.S.: a white, curdy precipitate occurs. Add to another 1 cc. portion of the choline solution a few drops of tannic acid T.S.: no precipitate should form.

Dry about 0.5 Gm. of choline dihydrogen citrate, accurately weighed, in vacuum over phosphorus pentoxide for 24 hours: the loss in weight does not exceed 0.25 per cent. Ash about 0.5 Gm. of choline dihydrogen citrate, accurately weighed: the residue does not exceed 0.05 per cent.

Weigh, accurately, about 0.2 Gm. of choline chloride, U. S. P. Reference Standard, and dilute to 100 cc. with water in a volumetric flask. Weigh, accurately, about 0.45 Gm. of choline dihydrogen citrate and dilute to 100 cc. with water in a volumetric flask. Transfer 0.5, 1.5, 2.5, 4.0 and 5.0 cc., respectively, of the standard solution to five conical 15 cc. centrifuge tubes. Transfer 1.5 cc. and 4.0 cc. of the test solution to two additional centrifuge tubes. Add 1.4 cc. of 6 normal hydrochloric acid to each tube and dilute to 7 cc. with water. Dissolve 2.0 Gm. of ammonium reineckate (U. S. P. XIII, p. 741) in 100 cc. of 1.2 normal hydrochloric acid and filter. Add to each centrifuge tube, slowly, with stirring, 5 cc. of the Reinecke salt solution. Let stand 30 minutes, with occasional stirring, and then centrifuge for 15 minutes at 2500 r.p.m. Decant the excess liquid, allow the tube to drain and carefully wipe the lip free of any solution. Wash the residue with 3 cc. of cooled 1.2 normal hydrochloric acid by pouring it into the centrifuge tube down the stirring rod previously used. Stir the precipitate gently but avoid prolonged stirring. Centrifuge for 15 minutes at 2500 r.p.m., and again discard the supernatant liquid. Dissolve the precipitate of choline reineckate in 2 cc. of acetone and transfer the solution to a 10 cc. volumetric flask. Wash each centrifuge tube twice more with 2 cc. portions of acetone and transfer the washings to the volumetric flask. Dilute the contents of the flasks to the mark with acetone and read the light absorption on a spectrophotometer at 5260 Å. Establish a standard curve from the values obtained from the standard solutions. Obtain the concentration of the test solution by referring their absorption values to the standard curve: the choline content is not less than 98 per cent nor more than 102 per cent.

**CHOLINE DIHYDROGEN CITRATE SYRUP:** Transfer 5 cc. of the choline dihydrogen citrate syrup to a 250 cc. volumetric flask, using a pipette calibrated to contain. Wash out the syrup from the pipette with water, transfer the washings into the flask and dilute to 250 cc. Mix, and transfer 1.5 cc. and 3.0 cc. to two centrifuge tubes. Add 1.4 cc. of 6 normal hydrochloric acid to each tube and continue the assay as described above: the choline content is not less than 90 per cent nor more than 110 per cent of the claimed amount.

**COPARAFFINATE.**—A mixture of water insoluble isoparaffinic acids partially neutralized with *isooctyl* hydroxy-benzyl-dialkyl amines.

Coparaffinate is a viscid, dark brown, oily liquid having a characteristic odor of burnt petroleum. It is immiscible with water; freely miscible with

alcohol, volatile oil and fixed oil. The specific gravity is from 0.970 to 0.980 at 25 C.

Place about 2 cc. of coparaffinate in a glass stoppered cylinder, add 20 cc. of water, shake the contents for five minutes, filter through moistened paper and divide into two portions; to one portion add two drops of methyl red T.S.: a distinct red color persists; to the other portion add two drops of thymol blue T.S.: a distinct yellow color persists.

***meta*-CRESYLACETATE.**— $C_9H_{10}O_2$ .—M. W. 150.17—

*Meta*-Cresylacetate occurs as a colorless oily liquid, possessing a characteristic odor. It is practically insoluble in water, but soluble in the ordinary organic solvents and in fixed and volatile oils. It is volatile with steam.

Shake 10 cc. of *meta*-cresylacetate with 100 cc. of water for one minute and filter through a wet filter; the filtrate has a neutral reaction and does not produce a violet color with ferric chloride T.S. or a turbidity with silver nitrate T.S. Evaporate 10 cc. of *meta*-cresylacetate in a tared porcelain dish and ignite: the residue is negligible.

**CYCLOBARBITAL.**— $C_{12}H_{16}N_2O_3$ .—M. W. 236.26.— $5\Delta^1$ -cyclohexenyl-5-ethyl barbituric acid.

Cyclobarbitol occurs as a white, crystalline, odorless powder, with a bitter taste. It is readily soluble in alcohol, about 1 in 5, and ether, about 1 in 10 and very slightly soluble in benzene and cold water. A saturated aqueous solution is acid to litmus paper. It melts at  $171-174^\circ$  C.

Dissolve 0.1 Gm. in 1 cc. of sulfuric acid: the liquid assumes a yellow color, changing quickly to orange, and finally to red. Place 0.3 Gm. in a 25 cc. glass stoppered cylinder, add 1 cc. sodium hydroxide T.S. and 5 cc. water, shake the contents for one minute, filter through paper and divide into two portions: the solution yields a white precipitate with 1 cc. of mercuric bichloride T.S., soluble in 5 cc. of diluted ammonia solution; the solution yields a white precipitate with 2 cc. of silver nitrate T.S., soluble in 5 cc. of diluted ammonia solution. Boil 0.5 Gm. with 5 cc. of a 20 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia.

Boil 0.5 Gm. with 50 cc. of water for two minutes; no odor develops; cool and filter: separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate T.S. (*sulfate*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Ash about 1 Gm. accurately weighed: there is not more than 0.01 per cent residue.

Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide, using thymolphthalein T.S. as an indicator: the amount of tenth-normal sodium hydroxide consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent of cyclobarbitol.

**DEHYDROCHOLIC ACID.**— $C_{24}H_{34}O_5$ .—M. W. 402.51.—An oxidation product of cholic acid derived from natural bile acids.

Dehydrocholic acid occurs as a fine, colorless, crystalline powder with a bitter taste. It is sparingly soluble in alcohol and glacial acetic acid. It melts at  $233-235^\circ$  C.

Boil about 1 Gm. of dehydrocholic acid with 100 cc. of water for two minutes; no odor develops. Cool and filter. Separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate T.S. (*sulfate*); no turbidity with 1 cc. of diluted sulfuric acid (*soluble barium compounds*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 1 Gm. of dehydrocholic acid accurately weighed, at 100 C.: The loss in weight does not exceed 1.5 per cent. Incinerate about 1 Gm. of dehydrocholic acid, accurately weighed: the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm., accurately weighed, in 40 cc. of previously neutralized alcohol, dilute with about one-half the volume of water and titrate with tenth-normal sodium hydroxide solution using phenolphthalein as an indicator. The amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent nor more than 101.5 per cent.

**d-DESOXYEPHEDRINE HYDROCHLORIDE.—No-**  
**rocin Hydrochloride-Endo.**— $C_{10}H_{15}N.HCl$ .—M. W. 185.69.  
—The hydrochloride of *d*-1-phenyl-2-methylaminopropane.

*d*-Desoxyephedrine hydrochloride occurs as a fine, white, odorless, crystalline powder, possessing a bitter taste. It is unaffected by light. It is soluble in alcohol, chloroform and water, but insoluble in ether. *d*-Desoxyephedrine hydrochloride melts between 170° and 175° C. A 1 per cent aqueous solution is neutral or slightly acid to blue litmus paper and has a specific rotation,  $[\alpha]_D^{25}$ , not less than + 14° nor more than + 20°, when the measurement is made on a solution of the salt (previously dried for 18 hours over sulfuric acid), contained in a 200 mm. tube.

Dissolve 0.3 Gm. of *d*-desoxyephedrine hydrochloride, accurately weighed, in 10 cc. of water and add 1 drop of methyl red T.S. If the solution is pink, it is changed to yellow by the addition of not more than 1.5 cc. of fiftieth-normal sodium hydroxide. Dissolve 50 mg. of the salt in 40 cc. of water and add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride T.S.: no turbidity develops within 10 minutes.

Prepare a 1 per cent aqueous solution of *d*-desoxyephedrine hydrochloride to be used for the following qualitative identification tests: It responds to the test for chloride. There is no change in color on the addition of ferric chloride T.S. (difference from epinephrine and phenylephrine). There is no detectable odor of carbylamine when a portion of the solution is heated to boiling with alcoholic potassium hydroxide T.S. and chloroform (difference from amphetamine, phenylpropanolamine and Tuamine). Mercuric potassium iodide T.S. yields an amorphous precipitate (difference from amphetamine, ephedrine, epinephrine, phenylephrine, phenylpropanolamine and Tuamine, which yield no precipitate; and from naphazoline, which yields a crystalline precipitate). Mercuric bichloride T.S. gives a crystalline precipitate (difference from amphetamine, ephedrine, epinephrine, phenylephrine, phenylpropanolamine and Tuamine, which give no precipitate; and from naphazoline, which gives an amorphous precipitate). Sodium hypochlorite T.S. gives a precipitate (difference from epinephrine and phenylephrine). Phosphotungstic acid T.S. yields a white precipitate (difference from epinephrine and phenylephrine, which give no precipitate; and from naphazoline, which gives a flesh colored precipitate). Iodine T.S. gives a brown precipitate immediately (difference from amphetamine, ephedrine, phenylpropylmethylamine and Tuamine, which give a brown precipitate upon adding an excess of iodine T.S.; and from epinephrine, phenylephrine and phenylpropanolamine, which give no precipitate). Tannic acid T.S. gives no precipitate (difference from phenylpropylmethylamine). A 1 per cent solution of picrolonic acid yields a precipitate (difference from ephedrine, epinephrine, phenylephrine and phenylpropanolamine). Platinic chloride T.S. gives a precipitate (difference from amphetamine, ephedrine, epinephrine, phenylephrine, phenylpropanolamine, phenylpropylmethylamine and Tuamine). A 1 per cent solution of phosphomolybdic acid yields a yellow precipitate (difference from naphazoline, which yields a tan-colored precipitate; from epinephrine, which yields a brown-colored solution; and from phenylephrine, which does not react). Picric acid T.S. gives a crystalline precipitate (difference from amphetamine, ephedrine, epinephrine, phenylephrine, phenylpropanolamine and Tuamine, which give no precipitate; and from phenylpropylmethylamine, which gives an amorphous precipitate).

Dry 0.25 Gm. of *d*-desoxyephedrine hydrochloride, accurately weighed, over sulfuric acid for 18 hours: the loss in weight does not exceed 0.2 per cent. Ignite 0.25 Gm. of *d*-desoxyephedrine hydrochloride, accurately weighed: the residue does not exceed 0.1 per cent.

Transfer about 50 mg. of *d*-desoxyephedrine hydrochloride, accurately



weighed and previously dried over sulfuric acid for 18 hours, to a 100 cc. micro-Kjeldahl digestion flask and add 20 cc. of distilled water. Connect the apparatus and add 20 cc. of 50 per cent sodium hydroxide solution. Distil with a rapid current of steam until about 150 to 200 cc. of distillate has been collected in a beaker containing 20 cc. of fiftieth-normal sulfuric acid solution and 2 drops of methyl red T.S. Titrate the excess acid with fiftieth-normal sodium hydroxide to a salmon-pink endpoint. Each cc. of fiftieth-normal sulfuric acid solution is equivalent to 0.002985 Gm. of anhydrous desoxyephedrine base: the amount of *d*-desoxyephedrine base found is not less than 79.5 nor more than 80.5 per cent.

Transfer about 0.1 Gm. of *d*-desoxyephedrine hydrochloride, accurately weighed and previously dried over sulfuric acid for 18 hours, to a beaker, and determine the chlorine content by following the method outlined for the assay of Sodium Chloride-U. S. P. Each cc. of tenth-normal silver nitrate is equivalent to 0.003546 Gm. of chlorine: the chlorine content found is not less than 18.9 nor more than 19.2 per cent.

### DIALLYLBARBITURIC ACID.— $C_{10}H_{12}N_2O_3$ .—M. W. 208.21.

Diallylbarbituric acid occurs as a fine, white crystalline powder, with a slightly bitter taste. It is completely soluble in alcohol and ether; very slightly soluble in cold water; and insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Diallylbarbituric acid melts at 171-173° C.

Place approximately 0.3 Gm. diallylbarbituric acid in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. normal sodium hydroxide solution and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions. To one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in 10 cc. of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in 5 cc. of diluted ammonia solution. Boil 0.5 Gm. with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with the evolution of ammonia. Dissolve 0.1 Gm. in 1 cc. of sulfuric acid: the liquid assumes a yellow color, changing slowly to a brownish-red, finally to a dark red. Place 1 Gm. in a 25 cc. glass stoppered cylinder, add 10 cc. of water, shake for one minute, filter through paper and divide into two portions; to one portion add 0.5 cc. of bromine T.S.: an immediate discoloration occurs; to the other portion add 0.1 cc. of potassium permanganate T.S.: a yellow color appears immediately.

Boil 0.5 Gm. of diallylbarbituric acid with 50 cc. of water for two minutes: no odor develops. Cool and filter. Separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*chloride*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate T.S. (*sulfate*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Ash about 1 Gm. of diallylbarbituric acid accurately weighed: the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol; dilute with an equal volume of water; and titrate with tenth-normal sodium hydroxide solution, using thymolphthalein T.S. as an indicator: the amount of tenth-normal sodium hydroxide solution consumed corresponds to not less than 98.5 per cent, nor more than 101.5 per cent of diallylbarbituric acid.

### DIBUCAINE HYDROCHLORIDE.— $C_{20}H_{29}N_3O_2$ .—M. W. 343.46.—2-Butoxy-4-( $\beta$ -diethylaminoethylamido) carboxyquinoline Hydrochloride.

Dibucaine hydrochloride occurs as a fine, white, crystalline, odorless, hygroscopic powder. It is very soluble in water, (about 2 in 1); freely soluble in alcohol; soluble in acetone and chloroform; slightly soluble in benzene, ethyl acetate and toluene on warming, but with difficulty in the cold. Its aqueous solution, about 1 in 20, is faintly alkaline to litmus, producing a definite anesthesia on the tongue. Dibucaine hydrochloride "melts" at 90 to 98 C.

Transfer about 0.5 Gm. of dibucaine hydrochloride to a suitable

Squibb separatory funnel, add 25 cc. of water, followed by the addition of 2 cc. of normal sodium hydroxide solution and extract with three successive portions of purified petroleum benzine, using 25 cc., 20. and 10 cc., respectively; evaporate the combined petroleum benzine extracts to dryness; the crystals melt at not less than 64° C. Dibucaine base fluoresces with the more common oxygen containing acids. Dissolve about 0.5 Gm. of dibucaine hydrochloride in 50 cc. of water, add 0.2 Gm. of potassium perchlorate previously dissolved in 25 cc. of water and allow to stand several hours: the crystals of dibucaine perchlorate crystallized from water melt at 130° to 132° C. Dissolve about 0.5 Gm. of dibucaine hydrochloride in 50 cc. of water; separate portions of 10 cc. each yield on the addition of 1 cc. of nitric acid and 2 cc. of silver nitrate T.S. a white precipitate, which, after decantation of the supernatant fluid, is soluble in an excess of diluted ammonia solution; no turbidity with 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride T.S. (sulfate); no color or precipitate on saturation with hydrogen sulfide (salts of heavy metals).

Dry about 0.5 Gm. of dibucaine hydrochloride, accurately weighed, over sulfuric acid in a desiccator for 48 hours: the loss does not exceed 2.5 per cent. Incinerate about 0.5 Gm., accurately weighed: the residue is not more than 0.1 per cent. Transfer about 0.5 Gm. to a 400 cc. beaker, add 75 cc. of water, followed by the addition of 25 cc. of silver nitrate T.S. and 1 cc. of nitric acid, subsequently boil, with continuous stirring, and allow to cool in a dark place. Collect the precipitate of silver chloride in a Gooch crucible, wash with diluted nitric acid, followed by alcohol and ether; finally dry to constant weight at 105°C.: the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 9.5 per cent nor more than 9.7 per cent, calculated to the dried substance. Transfer about 0.3 Gm., accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by the addition of 2 cc. of sodium hydroxide T.S., extract with six successive portions of chloroform, using 50 cc., 25 cc., 20 cc., 15 cc., 10 cc. and 10 cc., respectively, wash the combined chloroform solution with 15 cc. of water and evaporate to a thick oil in a stream of warm air; dry over sulfuric acid in a partially exhausted desiccator; dissolve the oily residue in about 10 cc. of previously neutralized alcohol; warm slightly; add 10 cc. of tenth-normal hydrochloric acid solution, followed by the addition of an equal volume of water; determine the excess of acid by titration with fiftieth-normal sodium hydroxide solution, using methyl red T.S. as an indicator: the amount of tenth-normal hydrochloric acid solution consumed corresponds to not less than 88.5 per cent nor more than 90.5 per cent butoxydiethylaminoethyl amide of quinoline carboxylic acid calculated to the dried substance.

**DICUMAROL.**— $C_{19}H_{12}O_6$ .—M. W. 336.286.—3,3'-methylenbis(4-hydroxycoumarin).

Dicumarol occurs as a white or slightly buff colored crystalline powder. It melts in the range 287-293°C. It is soluble in aqueous alkalis and pyridine; slightly soluble in benzene and chloroform; and practically insoluble in water, alcohol, and ether.

Dissolve 0.1 Gm. of Dicumarol in 10 cc. of sodium hydroxide T.S. and allow the solution to stand: it gradually darkens to a deep brown.

Dissolve 0.2 Gm. of Dicumarol in 5 cc. of hot pyridine. Cool, and add 2 cc. of acetic anhydride. After crystallization of the derivative is complete, filter, wash with alcohol and recrystallize from benzene. The product melts between 249 and 252° C. with decomposition.

Suspend 0.1 Gm. of Dicumarol in 10 cc. of water, heat to boiling, and filter while hot. Cool the filtrate and add 2 drops of silver ammonium nitrate T.S. to 5 cc. of the clear filtrate: no precipitate forms (*absence of formaldehyde and chlorides*).

Add 1 drop of ferric chloride T.S. to the remaining 5 cc. of filtrate: no color develops (*absence of salicylates and 4-hydroxycoumarin*).

Dissolve 1 Gm. of Dicumarol in enough sodium hydroxide T.S. to give complete solution, and dilute to 20 cc. with water. Add 5 drops of sodium sulfide T.S.: no more turbidity develops than corresponds to 30 ppm. of lead (U.S.P. XIII).

Dry 0.5 Gm. of Dicumarol, accurately weighed, for two hours at 100° C.: the loss in weight does not exceed 0.5 per cent.

Ash about 0.2 Gm. of Dicumarol, accurately weighed: the amount of residue is negligible.

Transfer about 0.3 Gm. of Dicumarol, accurately weighed to a 100 cc. beaker. Add 5 cc. of sodium hydroxide T.S. and then dilute with water to about 50 cc. Acidify with diluted hydrochloric acid, cool in an ice bath and filter while cold through a tared Gooch crucible. Wash with a small amount of ice water and dry at 100° C. to constant weight: the Dicumarol content is not less than 97.5 per cent nor more than 102.5 per cent.

**DIENESTROL.**— $C_{18}H_{18}O_2$ .—M. W. 266.32.—3,4-bis (p-hydroxyphenyl)-2,4-hexadiene.

Dienestrol occurs as colorless or white needle-like crystals or as a white crystalline powder. It is readily soluble in acetone, alcohol, ether, methanol and propylene glycol and in dilute aqueous sodium hydroxide solution; it is soluble in chloroform and practically insoluble in water and dilute mineral acids. It melts at 229° to 230° C.

Dissolve 10 mg. of dienestrol in 0.5 cc. of alcohol that is warm enough to completely dissolve the compound; cool and add 1 cc. of concentrated hydrochloric acid and approximately 50 mg. of vanillin: a blue color is produced immediately, which persists on dilution with water but disappears on the addition of alkali (*differentiation from hexestrol and diethylstilbestrol, which produce no color*).

A solution of 0.1 Gm. of dienestrol in 10 cc. of warm normal sodium hydroxide is clear; on dilution with 20 cc. of distilled water and addition of 5 drops of 10 per cent sodium sulfide solution, the mixture does not darken more than a control solution containing 0.02 mg. of added lead.

When dried to constant weight at 100°C., an accurately weighed sample of dienestrol loses not more than 0.5 per cent in weight. It yields not more than 0.05 per cent of residue on ignition.

Transfer to a suitable flask about 0.5 Gm. of previously dried dienestrol, accurately weighed, and add 2 cc. of acetic anhydride and 4 cc. of dry pyridine. Boil the mixture under a reflux condenser for 15 minutes; cool, add 50 to 60 cc. of distilled water and shake the flask and contents thoroughly. Stopper the flask and place it in the refrigerator over night. Collect the precipitate on a suitable tared filter and wash it with four 15 cc. portions of distilled water. Dry the precipitate at 75 to 80°C. for five hours, cool and weigh. The weight of the dry dienestrol diacetate obtained, when multiplied by 0.760, corresponds to a dienestrol content of not less than 98 per cent and not more than 101 per cent. The dienestrol diacetate obtained melts at 119° to 120°C.

**DIETHYLSTILBESTROL DIPROPIONATE.**—The dipropionyl ester of  $\alpha,\alpha'$ -diethyl-4,4'-stilbenediol.— $C_{24}H_{28}O_4$ —M. W. 380.46.

Diethylstilbestrol dipropionate occurs as an odorless, tasteless, white, crystalline powder which melts at 105-107° C. It is readily soluble in acetone, benzene, ether, chloroform, hot ethyl alcohol and hot methyl alcohol; soluble in vegetable oils; very slightly soluble in water and dilute mineral acids; and insoluble in aqueous alkalies. A suspension of 0.1 Gm. of diethylstilbestrol dipropionate in 10 cc. of diluted alcohol is neutral to litmus paper.

Dissolve 10 mg. of diethylstilbestrol dipropionate in 2 cc. of concentrated sulfuric acid: an orange color is produced which disappears on dilution with water. Add 1 cc. of 50 per cent solution of antimony pentachloride in dry alcohol-free chloroform to 5 cc. of a dilute solution of diethylstilbestrol dipropionate in the same solvent: a red colored solution is produced. The residue obtained in the assay for diethylstilbestrol dipropionate melts at 168-171°C. and responds to tests for diethylstilbestrol.

Dry an accurately weighed specimen of diethylstilbestrol dipropionate to constant weight in a partial vacuum at 80° C.: the loss in weight does not exceed 0.5 per cent. Ignite an accurately weighed specimen of diethylstilbestrol dipropionate after the addition of concentrated sulfuric acid: the residue does not exceed 0.05 per cent.

Dissolve approximately 0.3 Gm. of diethylstilbestrol dipropionate, accurately weighed, in 10 cc. of a 15 per cent solution of potassium hydroxide in methyl alcohol and heat under reflux for 30 minutes. Cool, dilute with 100 cc. of water, transfer to a separator and acidify with dilute hydrochloric acid. Extract the mixture with four separate portions of ether, combining the ether extracts; wash the ether solution with three separate portions of 5 per cent sodium bicarbonate solution and once with water; decant the ether solution through a small cotton plug into a tared beaker; rinse the separatory funnel and cotton plug with fresh ether and evaporate the ether extract in a stream of warm air. Dry the residue to constant weight at 75-80°C.: the weight of the diethylstilbestrol obtained, multiplied by the factor 1.418, is equivalent to not less than 98 per cent nor more than 100.5 per cent of the weight of the specimen.

**DIGALEN-Hoffmann-La Roche.**—The cardioactive principles of digitalis as isolated by Cloetta.

Digalen is a colorless or slightly yellowish liquid of an agreeable aromatic odor with a sweet taste which subsequently becomes bitter.

The active derivative contained in Digalen is an amorphous, white or slightly yellow powder. It dissolves readily in alcohol and chloroform, and less readily in ether. It has an intensely bitter taste and causes violent sneezing, when introduced into the nose.

To 2 cc. of Digalen add a few drops of diluted acetic acid and extract with chloroform. Evaporate the chloroform extract and dissolve the residue in about 2 cc. of glacial acetic acid containing a trace of ferric chloride. To this solution add strong sulfuric acid without mixing so as to form a separate layer: a brown ring forms between the two layers which becomes broader after some hours and expands toward the top in a blue-green to black shade, and toward the bottom in a reddish-brown one. The acetic acid finally acquires a dark green-blue color.

**DIGIFOLIN-Ciba.**—A digitalis preparation containing the therapeutically desirable constituents of digitalis leaf.

Digifolin is almost colorless and odorless, with a slightly bitter taste. It is an amorphous brownish powder, soluble in water, methyl alcohol and ethyl alcohol; insoluble in ether and petroleum ether.

Prepare two solutions: (A) Dissolve 5 Gm. ferric sulfate in 100 cc. water, filter and add 5 cc. of the filtrate to 500 cc. of pure glacial acetic acid; (B) add (*caution!*) 5 cc. of the ferric sulfate solution to 500 cc. pure sulfuric acid. Dissolve a trace of Digifolin in 5 cc. of solution A and layer this solution carefully on 5 cc. of solution B: at the point of contact, a dark band appears; the lower layer assumes a red color and the upper layer a bluish-green color; on standing, the bluish-green layer turns to indigo-blue.

**DIGILANID-Sandoz.**—A mixture of the isomorphous crystallized cardio-active glycosides, lanatoside-A ( $C_{49}H_{76}O_{19}$ ), lanatoside-B ( $C_{49}H_{76}O_{20}$ ) and lanatoside-C ( $C_{49}H_{76}O_{20}$ ), obtained from the leaves of *Digitalis lanata*. The three components are present in the mixture in the proportions in which they occur in the crude drug, namely about 47 per cent lanatoside-A, 16 per cent lanatoside-B and 37 per cent lanatoside-C.

Air dried Digilanid occurs as a white, odorless powder, possessing a bitter taste; soluble in methanol, 1 in 20; very slightly soluble in water,

1 in 10,000; and insoluble in ether. Digilanid, when heated rapidly, melts with decomposition above 245°C.

Transfer 2 mg. of Digilanid to a 15 cm. test tube and add 4 cc. of glacial acetic acid and one drop of ferric chloride T.S. Add from a pipet 4 cc. of sulfuric acid to underlay the acetic acid solution and allow to stand one hour: a blue color appears in the upper zone (*digitoxose*) and a violet-brown in the lower zone (*mixture of aglucones*). Transfer about 0.02 Gm. of Digilanid to a 10 cm. test tube and add 1 cc. each of water, methanol and lead acetate T.S.: no immediate precipitate or coloration occurs (*appreciable amounts of tannoid substances*). Transfer about 20 mg. of Digilanid to a test tube and add 2 cc. of methanol, 2 cc. of water and 0.5 cc. of alkaline cupric tartrate T.S. and heat for ten seconds: no turbidity appears (*free reducing sugars*).

Transfer about 20 mg. of Digilanid, dried under vacuum and accurately weighed, to a 10 cc. volumetric flask and make up to volume with ethanol. Mix, transfer to a 2 dcm. polarimeter tube and observe the angular rotation, using sodium light at 25° C.: the specific rotation

<sup>25</sup>  
[α] — is not less than + 32.0 and not more than + 33.8.  
D

Transfer about 0.2 Gm. of Digilanid, dried under vacuum and accurately weighed, to a 150 cc. glass stoppered Erlenmeyer flask and cautiously add 40 cc. of methanol and 20 cc. of tenth-normal sodium hydroxide. Stopper the flask and allow to stand 72 hours. To a similar flask add 40 cc. of ethanol and 20 cc. of tenth-normal sodium hydroxide, stopper and allow to stand 72 hours. Titrate both solutions with tenth-normal hydrochloric acid, using phenolphthalein T.S. as indicator: the volume of tenth-normal sodium hydroxide required by 1 Gm. of Digilanid is not less than 20.0 and not more than 23.0 cc.

Transfer about 0.2 Gm. of Digilanid, dried under vacuum and accurately weighed, to a 250 cc. separator, add 100 cc. of chloroform, 20 cc. of methanol and 100 cc. of water, and shake at 25°C. for one minute. Separate the layers and evaporate each in vacuo to dryness. Wash the residues into tared weighing bottles with methanol and again evaporate to dryness in vacuo at 55°C., and weigh: The weight of the residue from the chloroform divided by the sum of the weights of the residues is not less than 0.60 and not more than 0.63.

**DIGITAN-Merck.**—A purified extract of digitalis containing the active principles in the same proportions as they exist in the whole leaf. In digitan, 85 per cent of the inactive substances present in the ordinary extract have been removed and it is free from digitonin.

Digitan is a greenish-yellow, odorless, bitter powder. The active constituents of Digitan are insoluble in cold water and diluted acids, but are easily soluble in weak alkalis.

Digitan responds to the following identity test: If 0.1 Gm. of Digitan is underlaid with about 3 cc. of glacial acetic acid which contains 1 per cent of a 5 per cent solution of ferric sulfate, there appears a red band (*presence of digitalin*) and above this another, at first bright green, later changing to dark green and finally blue (*presence of digitoxin*).

**DIHYDROXY ALUMINUM AMINOACETATE.**— $C_2H_6O_4-NA_1$ .—M. W. 135.05.—Basic aluminum aminoacetate.—A basic aluminum salt of glycine containing small amounts of aluminum hydroxide and glycine.

Basic aluminum aminoacetate is a white, odorless powder with a faint sweet taste. It is insoluble in water and organic solvents, but soluble in dilute mineral acids and solutions of fixed alkalies to yield a cloudy solution which clarifies on heating.

Dry two grams of basic aluminum aminoacetate, accurately weighed,

to constant weight at 130° C. This requires two to three days drying. The loss in weight does not exceed 14.5 per cent.

Prepare a suspension of one gram of finely ground basic aluminum aminoacetate in a glass stoppered flask containing 25 cc. of distilled water. Mix the contents for five minutes, and then let stand for five minutes. The pH should be 6.5 to 7.5.

Transfer 0.2 Gm. of finely ground basic aluminum aminoacetate, accurately weighed, to a glass stoppered flask containing 25 cc. of tenth-normal hydrochloric acid. Agitate the mixture vigorously for five minutes, and then let it stand for five minutes. The pH must be above 3.0.

To 20 cc. of an aqueous suspension (1 in 25) of basic aluminum aminoacetate add hydrochloric acid dropwise until the compound just dissolves to form a clear solution. Divide the solution into two equal portions. To one portion add an excess of diluted ammonia solution: a white flocculent precipitate of aluminum hydroxide is formed which is insoluble in an excess of ammonia but soluble in sodium hydroxide T.S. To the other portion add one drop of liquified phenol and 5 cc. of sodium hypochlorite T.S.: a blue color is produced, characteristic of glycine.

Basic aluminum aminoacetate shows no heavy metals when subjected to the test outlined in the *U. S. P. XIII*, p. 657. Basic aluminum aminoacetate should be free of mercury when a solution containing one gram of the compound dissolved in 10 cc. diluted hydrochloric acid is shaken with 10 cc. of a solution of dithizone in carbon tetrachloride (concentration 2 mg. per 100 cc.): The carbon tetrachloride layer does not turn orange. (Feigl, F., *Qualitative Analysis by Spot Tests*, 3rd ed., Elsevier, p. 49.)

Suspend 5 Gm. of basic aluminum aminoacetate in 100 cc. of tenth-normal potassium permanganate acidified with 10 cc. of concentrated sulfuric acid. Reflux the mixture for 30 minutes and distil a 10 cc. sample. The distillate must be free from acetone as shown by the nitroprusside test, *N. F. VIII*, p. 20.

Add 0.25 Gm. of finely ground basic aluminum aminoacetate to 50 cc. tenth-normal hydrochloric acid. Allow to stand 10 minutes with occasional agitation. At the end of 10 minutes back titrate the excess acid with tenth-normal sodium hydroxide to a pH of 3.8 using bromphenol blue T.S. as an indicator. One gram of basic aluminum aminoacetate neutralizes at room temperature not less than 125 cc. and not more than 175 cc. of tenth-normal hydrochloric acid under these conditions.

Transfer about one gram of dried basic aluminum aminoacetate, accurately weighed, to a platinum dish. Add 5 cc. nitric acid and 2 cc. of sulfuric acid (1:1). Fume off the acids and ignite in a muffle furnace at 1200° to 1500° C. Dissolve the residue in 10 cc. of hydrochloric acid and 5 cc. of sulfuric acid (1:1) and transfer to a 600 cc. beaker. Dilute with water to 400 cc. and add strong ammonia solution until the solution is just basic to methyl red T.S. Heat to boiling, filter and wash the precipitate with hot water until the washings are free from chloride. Dry the precipitate, ignite it at 1200°-1500° C. to constant weight, cool and weigh the aluminum oxide so obtained. The calculated aluminum oxide content of dry basic aluminum aminoacetate is not less than 34.9 per cent and not greater than 38.7 per cent.

Determine the nitrogen content by the semimicro Kjeldahl method, *U. S. P. XIII*, p. 673, using 0.1 Gm. of dried basic aluminum aminoacetate, accurately weighed. The per cent of nitrogen present in dry basic aluminum aminoacetate is not less than 9.8 or greater than 10.8 per cent.

### DIIDO-HYDROXYQUINOLINE. — $C_9H_5I_2NO$ . — M. W. 397.34.—5,7-Diiodo-8-hydroxyquinoline.

Diiodo-hydroxyquinoline occurs as a yellowish brown, practically odorless powder. It is almost insoluble in water; sparingly soluble in alcohol, ether and acetone; soluble in hot pyridine and in hot dioxane. Diiodo-hydroxyquinoline melts between 200° and 215° C. with extensive decomposition.

Warm a few crystals of diiodo-hydroxyquinoline with 1 cc. of concentrated sulfuric acid: vapors of iodine are evolved. Heat 0.5 Gm. of diiodo-hydroxyquinoline mixed with 5 Gm. of anhydrous sodium carbonate

in a deep crucible; cool; extract the mixture in 10 cc. of water; acidify with diluted nitric acid. Filter and add 13 cc. of tenth-normal silver nitrate to the filtrate. Shake to coagulate the precipitate and filter. Add 1 cc. of tenth-normal silver nitrate to the filtrate, shake and filter through a fresh filter paper. Wash the precipitate on the filter: a yellow color is observed (*distinction from Vioform, which gives a white precipitate*).

Dry 1 Gm. of diiodo-hydroxyquinoline over phosphorous pentoxide for 24 hours: the loss in weight is less than 0.1 per cent.

Incinerate about 1 Gm. of diiodo-hydroxyquinoline: the ash is not over 0.5 per cent.

Mix about 0.15 Gm. of diiodo-hydroxyquinoline, accurately weighed, in a nickel crucible with 5 Gm. of anhydrous potassium carbonate. Mix thoroughly with a dry stirring rod, settle the mixture by tapping the crucible, overlay with 5 Gm. of potassium carbonate (or sodium carbonate) and ignite at about 600°C. for from six to eight minutes. Cool, transfer the crucible to a 500 cc. wide mouth conical flask and extract with about 20 cc. of distilled water. Acidify the solution carefully, dropwise, with five normal hydrochloric acid (about 30 cc.) Filter the solution quantitatively into a 250 cc. glass stoppered flask, using two 20 cc. portions of water to rinse the flask and filter paper. The volume at this point should be about 100 cc. Add a cooled mixture of 35 cc. of hydrochloric acid, 35 cc. of distilled water, and add 10 cc. of redistilled chloroform. Titrate with fiftieth-molar potassium iodate to the disappearance of pink color in the chloroform layer (add iodate dropwise and shake vigorously near the endpoint). One cc. of fiftieth molar potassium iodate is equivalent to 0.005076 Gm. of iodine. Diiodo-hydroxyquinoline contains not less than 60.5 per cent nor more than 64.0 per cent of iodine.

**2,3-DIMERCAPTOPROPANOL IN OIL.**—A solution of 2,3-dimercaptopropanol 10 per cent in peanut oil, containing benzyl benzoate 20 per cent.

2,3-Dimercaptopropanol in oil is a yellow viscous solution possessing a pungent offensive odor. The benzyl benzoate and peanut oil used in the preparation of the solution meet with the requirements of the U.S. Pharmacopeia.

Dilute approximately 1 Gm. of 2,3-dimercaptopropanol in oil, accurately weighed by difference, with 15 cc. of chloroform and 50 cc. of methyl alcohol. Titrate the resulting solution with tenth-normal iodine solution to a permanent yellow color, or, if desired, add an excess of the iodine solution and back titrate with tenth-normal sodium thiosulfate solution. Each cc. of tenth-normal iodine solution is equivalent to 0.00621 Gm. of 2,3-dimercaptopropanol.

**DIPERODON HYDROCHLORIDE.**—Diothane Hydrochloride—Merrell.— $C_{22}H_{27}N_3O_4 \cdot HCl$ .—M. W. 433.92.—di-Phenylurethane of 1-Piperidinopropane-2,3-diol Hydrochloride.

Diothane Hydrochloride occurs as a fine, white crystalline, odorless powder; when applied to the tongue, it produces a bitter taste followed by a sense of numbness. It is stable in air at ordinary temperatures. Diothane hydrochloride is slightly soluble in water, acetone and ethyl acetate; soluble in alcohol; insoluble in benzene and ether. Its aqueous solution (1 in 100) is faintly acid to litmus. Diothane Hydrochloride melts at 195° to 200°C., with decomposition. From aqueous solutions, alkali carbonates and hydroxides precipitate the free base as a colorless oil, which does not solidify under ordinary conditions.

Dissolve about 0.5 Gm. of Diothane Hydrochloride in 50 cc. of water and use 5 cc. portions of it in the following tests. To one portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in an excess of diluted ammonia solution. To another portion add 0.2 cc. of diluted hydrochloric acid, 0.2 cc. of a 10 per cent solution of sodium nitrite and gradually mix with a solution of 0.2 Gm. of betanaphthol in 10 cc. of a 10 per

cent sodium hydroxide solution: a white precipitate, changing to a yellowish and finally to an orange color appears, increasing in intensity as the concentration of the betanaphthol becomes greater (*distinction from the anesthetics responding to the diazoreaction*). To a third portion add 5 drops of gold chloride T.S.: an orange-yellow precipitate appears (*distinction from cocaine and metycaine, which give lemon-yellow precipitates, and butacaine and procaine, which yield brown precipitates*). Dissolve about 0.1 Gm. of Diothane Hydrochloride in 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Saturate about 0.1 Gm. of Diothane Hydrochloride dissolved in 10 cc. of water with hydrogen sulfide: no color or precipitate results (*salts of heavy metals*).

Dry about 0.5 Gm. of Diothane Hydrochloride, accurately weighed, at 100°C. for six hours: the loss in weight does not exceed 0.5 per cent. Incinerate about 0.5 Gm. of Diothane Hydrochloride, accurately weighed: the residue is not more than 0.1 per cent. Transfer about 0.3 Gm. of Diothane Hydrochloride, accurately weighed, to a 500 cc. Kjeldahl flask, and determine the nitrogen content according to the official method described in *Methods of Analysis of the Association of Official Agricultural Chemists*, 6 ed., page 26, paragraph 25: the percentage of nitrogen corresponds to not less than 9.5 per cent, nor more than 9.8 per cent when calculated to the dried substance. Dissolve about 0.25 Gm. of Diothane Hydrochloride, accurately weighed, in 25 cc. of water, by warming, and transfer to a suitable Squibb separatory funnel, rinse twice using about 10 cc. of water, followed by the addition of 3 cc. of a dilute ammonium hydroxide (one part of diluted ammonia solution and ten parts of water), extract with four successive portions of ether using 20 cc. each; filter through a pledget of cotton and evaporate to a thick oil in a stream of warm air; dissolve the oily residue in about 25 cc. of previously neutralized alcohol; warm slightly; add 10 cc. of tenth normal hydrochloric acid solution, followed by the addition of 10 cc. of water; determine the excess of acid by titration with tenth-normal sodium hydroxide solution, using bromphenol blue T.S. as an indicator: the amount of tenth-normal hydrochloric acid consumed corresponds to not less than 90.5 per cent nor more than 92 per cent of piperidinopropanedioldi-phenylurethane when calculated to the dried substance. Transfer the ammoniacal aqueous portion from the foregoing extraction to a 400 cc. beaker and place on the steam-bath for three hours; add 100 cc. of water, followed by the addition of 1 cc. of nitric acid and 25 cc. of silver nitrate T.S.; subsequently boil with continuous stirring and allow to cool in a dark place. Collect the precipitate of silver chloride on a Gooch crucible, wash with diluted nitric acid and water, followed by alcohol and ether; finally dry to constant weight at 105°C.; the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 8.35 per cent, nor more than 8.45 per cent when calculated to the dried substance.

**DIPHENHYDRAMINE HYDROCHLORIDE.**— $C_{17}H_{22}ClNO$ .—M. W. 291.82.— $\beta$ -Dimethylaminoethyl benzohydril ether hydrochloride.—The hydrochloride of the diphenylmethyl ether of  $\beta$ -dimethylaminoethanol.

Diphenhydramine hydrochloride occurs as a white, crystalline powder, possessing a characteristic odor and a bitter taste. It melts within the range 166-170°C. It is very soluble in water, freely soluble in alcohol and in chloroform, and very slightly soluble in benzene and in ether. The  $pH$  of a 1 per cent solution is about 5.50.

Add 3 cc. of sulfuric acid to 0.1 Gm. of diphenhydramine hydrochloride: a yellow color develops immediately, which turns brownish-red upon standing.

Add 2 cc. of hydrochloric acid to 0.1 Gm. of diphenhydramine hydrochloride dissolved in 5 cc. of water. Boil for 3 minutes, cool on ice, filter, recrystallize from water and dry; the crystals melt at 65°C.

Add 3 drops of saturated Reinecke's salt solution to 2 cc. of a 1 per cent aqueous solution of diphenhydramine hydrochloride: a pink colored precipitate develops.

Dry 0.5 Gm. of diphenhydramine hydrochloride, accurately weighed,



at 110 C., for 4 hours: the loss in weight does not exceed 0.5 per cent.

Ash about 0.5 Gm. of diphenhydramine hydrochloride, accurately weighed; add 5 drops of sulfuric acid to the cooled mass and ignite: the amount of residue is not more than 0.05 per cent.

Dissolve 0.5 Gm. diphenhydramine hydrochloride in 5 cc. of water; add 1 cc. of 10 per cent sodium hydroxide and shake for 1 minute. Filter through a wetted filter paper until clear. Add to the filtrate 0.5 cc. hydrochloric acid and about 20 granules of about 20 mesh metallic zinc. Heat to boiling; allow to stand for 3 minutes, and decant the solution into another tube. Add 5 drops of 1 per cent aqueous solution of phenylhydrazine hydrochloride, heat almost to boiling, and then cool with tap water to room temperature. Add an equal volume of hydrochloric acid, followed by 5 drops of a 5 per cent aqueous solution of potassium ferricyanide. Mix thoroughly and allow the tube to stand in the dark for 30 minutes: no pink or red color develops in the liquid (*oxalate*).

Dissolve 0.5 Gm. of diphenhydramine hydrochloride in 10 cc. of water; neutralize with 1.5 cc. of sodium hydroxide solution. Add 1 cc. of acetic acid and 5 cc. of hydrogen sulfide solution: no more color develops than corresponds to 20 ppm. of lead.

Weigh accurately about 0.15 Gm. of diphenhydramine hydrochloride and transfer to 50 cc. of water in a separatory funnel. Add 10 cc. of 10 per cent sodium hydroxide solution, and extract with 25, 20, 15, and 10 cc. of ether. Wash the combined ether extracts with two 5 cc. portions of water. Saturate the water extracts with sodium chloride; reextract with 5 cc. of ether, and add to the main ether extract. Add two 5 cc. portions of tenth-normal sulfuric acid, and extract the diphenhydramine hydrochloride from the ether solution. Wash the ether solution with two 5 cc. portions of water, and combine with the acid washings. Titrate the acid solution with tenth-normal sodium hydroxide, using methyl red T.S. as the indicator. Each cc. of tenth-normal sodium hydroxide is equivalent to 0.02918 Gm. of diphenhydramine hydrochloride: the diphenhydramine hydrochloride content is not less than 98 per cent nor more than 102 per cent.

**DIPHENHYDRAMINE HYDROCHLORIDE KAPSEALS:** Weigh accurately the contents of 10 capsules. Weigh, accurately, 0.25 to 0.35 Gm. portions of this powder, suspend the powder in 50 cc. of water in a separatory funnel, and carry out the extraction and determination as described in the assay for diphenhydramine hydrochloride: the diphenhydramine hydrochloride content is not less than 98 per cent nor more than 102 per cent.

**DIPHENHYDRAMINE HYDROCHLORIDE ELIXIR:** Pipette 50 cc. of diphenhydramine hydrochloride elixir into a separatory funnel. Add 2 cc. of diluted hydrochloric acid to each sample, and extract with two 15 cc. portions of ether. Add 2 cc. of 40 per cent sodium hydroxide to the aqueous phase. Extract with 25, 20, 15, 10, 10, 10, and 10 cc. portions of ether; rinse the funnel each time with ether. Wash the combined ether extracts with two successive 5 cc. portions of water. Extract the water washings once with ether, and combine with the other ether extracts. Add 10 cc. of tenth-normal sulfuric acid, shake vigorously, and separate. Add 5 cc. more of the tenth-normal sulfuric acid and repeat the shaking. Combine the two acid extractions. Rinse the ether with two 5 cc. portions of water, and combine with the acid solution. Titrate with tenth-normal sodium hydroxide to a methyl red end point. Each cc. of tenth-normal sodium hydroxide is equivalent to 0.02918 Gm. of diphenhydramine hydrochloride: the diphenhydramine hydrochloride content is not less than 95 per cent nor more than 105 per cent.

**DYMIKAL-McNeil Labs.**—A mixture of three dyes containing crystal violet 46 per cent, brilliant green 31 per cent and acriflavine 23 per cent. It may be prepared by mechanical mixing of the three dyes in their solid state.

Dymixal powder is soluble in water, forming a neutral greenish blue solution which shows a yellow fluorescence under ultraviolet light.

The crystal violet used in the mixture meets the standards set forth for methylrosaniline chloride in the *U. S. P. XIII*, p. 326. The brilliant green used complies with the standards for brilliant green-N. N. R.

The acriflavine used meets the standards set forth for acriflavine in *N. F. VIII*, p. 25.

Prepare an adsorption column by tamping dry Celite No. 545 (Johns-Manville) into a glass tube approximately 8 mm. by 350 mm. Pour 5 cc. of an aqueous solution of Dymixal containing approximately 0.5 mg. of Dymixal onto the dry column and allow it to filter down the column aided by suction. Just before the last bit of liquid disappears from the top of the column add an aqueous solution of acetone (22% V/V) to develop the chromatogram. Bands of crystal violet, brilliant green and acriflavine appear on the column.

Dilute an aqueous solution of Dymixal accurately to a concentration of about 0.04 microgram per cubic centimeter of acriflavine. Measure the fluorescence of the solution in a photofluorometer using a solution of acriflavine, *N. F.*, 0.04 microgram per cubic centimeter, as a standard: the amount of acriflavine found corresponds to not less than 19 per cent nor more than 26 per cent.

Determine the quantities of crystal violet and brilliant green in Dymixal by measuring the light absorption (*E* instrumental) of appropriate dilutions in 50% V/V aqueous alcohol at wavelengths of 5800, 5900, 6000, 6100, 6200 and 6300 Å in a spectrophotometer. For comparison, determine the  $E_{\frac{1\%}{1 \text{ cm.}}}$  values for crystal violet alone and for brilliant green alone, using concentrations similar to those expected in the unknown solution. To calculate the  $E_{\frac{1\%}{1 \text{ cm.}}}$  values, divide the *E* instrumental values by the product of the cell thickness and the concentration used in grams per hundred cubic centimeters. Calculate the percentage of brilliant green and crystal violet present in the diluted solution from a set of equations, valid at each wavelength as follows:

$$E \text{ observed for Dymixal} = (X \text{ times } E_{\frac{1\%}{1 \text{ cm.}}} \text{ for crystal violet}) + (Y \text{ times } E_{\frac{1\%}{1 \text{ cm.}}} \text{ for brilliant green})$$

$100 \frac{X}{c}$  equals the percentage of crystal violet and  $100 \frac{Y}{c}$  represents the percentage of brilliant green, where *c* equals concentration in grams per hundred cubic centimeters of Dymixal measured: by this method, Dymixal contains not less than 42 per cent nor more than 48 per cent of crystal violet and not less than 27 per cent nor more than 35 per cent of brilliant green.

**EPINEPHRINE IN OIL SUSPENSION, 1:500.**—A 0.2 per cent suspension, containing 1 part of epinephrine *U. S. P.* to 500 parts of vegetable oil.

Epinephrine in oil occurs as a pale yellow to white milky suspension from which a white solid settles out on standing. Centrifuge an ampul of epinephrine in oil until the crystals have collected in the bottom, open the ampul, decant the clear oil, and wash the residue with two 1 cc. portions of acetone by decantation: the residue, dried at 75 C., melts above 215 C., when heated at a rate of 8 degrees per minute.

Transfer an accurately measured volume of epinephrine in oil, containing approximately 8 mg. of epinephrine to a centrifuge tube. Centrifuge, wash and dry as described above. Dissolve the residue in 0.40 cc. of normal hydrochloric acid, filter and polarize in a micro-polariscope tube. The specific rotation  $[\alpha]_{\frac{25}{D}}$  is between -50.0 and -53.5 degrees.

Shake 1.0 cc. of epinephrine in oil with 5.0 cc. of tenth-normal hydrochloric acid, add 20.0 cc. of distilled water, shake, filter through a paper previously moistened with water. Discard the first 5 cc. and save the remainder for the test. To 20.0 cc. of 0.5 per cent potassium iodate solution contained in a 50 cc. flask add 0.50 cc. of normal hydrochloric acid, warm to 38 C., and add 10.0 cc. of the filtrate. At the

same time, prepare a standard by the method described above, after adding 5.0 cc. of solution containing 8.0 mg. of U. S. P. epinephrine in 20.0 cc. of tenth-normal hydrochloric acid to 1.0 cc. of peanut oil. Warm the standard and sample solution for fifteen minutes at 38 C., cool to room temperature, and compare in a colorimeter. The epinephrine content should not be more than 2.15 nor less than 1.85 mg. per cc.

**ESTRIOL.**— $C_{18}H_{24}O_3$ .—M. W. 288.37.—3,16,17-trihydroxy- $\Delta$ -1,3,5-estratriene. A crystalline estrogenic steroid isolated from the urine of pregnant women.

Estriol occurs as a white, odorless, microcrystalline powder, practically insoluble in water, but soluble in alcohol, dioxane and oils. During heating on a hot stage of a microscope, a phase change occurs between 270° and 275° C. and the material melts sharply at 282° C. (rate of heating, 4° a minute — Kofler microscope heating stage). On heating for five hours in an Abderhalden drier at 80° C. under a vacuum of 2 mm., 20 mg. estriol loses no appreciable weight.

Transfer approximately 40 mg. of estriol, accurately weighed, to a 1 cc. microvolumetric flask; fill to the mark with freshly distilled dioxane and determine the optical rotation after the U. S. P. method, using a 2 dm. microtube. The specific rotation  $[\alpha]_{D}^{25}$  is + 58 degrees ( $\pm$  5 degrees).

Dissolve approximately 60 mg. of estriol, accurately weighed, in a mixture of pyridine (6 cc.) and acetic anhydride (2 cc.) and heat under a micro reflux condenser for twenty-four hours at 95° C. Transfer the solution to a 250 cc. flask containing 100 cc. of ice-cold water and titrate with tenth-normal sodium hydroxide: the acetic acid value is not more than 129 nor less than 121, equivalent to three acetylated hydroxyl groups. [A blank determination must be made for pyridine acetic acid and anhydride] (*J. Biol. Chem.* 91:655, 1931).

Dissolve approximately 40 mg. of estriol in a mixture of pyridine (6 cc.) and acetic anhydride (2 cc.) and heat under a micro reflux condenser for 21 hours at 95° C. Let stand at 37° C. for another 24 hours. Add 10 cc. of 50 per cent alcohol and evaporate under vacuum to a thick syrup. Add very gradually about 1 cc. of alcohol and set aside for crystallization. Filter the crystals and redissolve in 3 cc. of 95 per cent alcohol. Evaporate the alcohol and dissolve the residue in 4 cc. of pyridine. After addition of 16 cc. of water a white flocculent precipitate occurs; recrystallize twice from 90 per cent alcohol; dry the crystals in vacuum at 80° C. over phosphorus pentoxide: the melting point of the triacetate is 126° C. ( $\pm$  1 degree).

Ash about 2 mg. of estriol, accurately weighed, in a tared platinum micro boat: no residue should remain. Micro carbon and hydrogen analysis, according to Pregl's method, gives a carbon content of not more than 75.2 per cent, nor less than 74.6 per cent, and a hydrogen content of not more than 8.7 per cent, nor less than 8.0 per cent.

Estriol crystals exhibit a reddish fluorescence under filtered ultra-violet light.

The dosage forms of brands of estriol are biologically assayed, the assay being under control of the St. Louis University Committee.

**ETHINYL ESTRADIOL.**— $C_{20}H_{24}O_2$ .—M. W. 296.4.—17-Ethinyl-3,17-dihydroxy- $\Delta$ -1,3,5-estratriene.

Ethinyl estradiol occurs as a fine, white, odorless, crystalline powder, which melts at 141-146° C. It is soluble in acetone, alcohol, chloroform, dioxane and ether; soluble in vegetable oils, but practically insoluble in water; and soluble in solutions of sodium or potassium hydroxide.

An alcohol solution containing ethinyl estradiol, 0.05 mg. per cc., possesses strong light absorption at 2300A; exhibits an absorption

minimum at about 2480A and a characteristic maximum at about 2810A. ( $E \frac{1\%}{1 \text{ cm.}} = 71 \pm 0.5$ ).

The specific rotation,  $[\alpha]_D^{25}$ , of ethinyl estradiol, determined in a solution in dioxane containing in each 10 cc., 0.1 Gm. of ethinyl estradiol, using a 100 mm. tube, is not less than +1 degree nor more than +10 degrees.

Dissolve about 2 mg. of ethinyl estradiol in 2 cc. of sulfuric acid: the solution is orange-red colored by transmitted light and shows a yellow-green fluorescence in reflected light. Divide the sulfuric acid solution into two portions, add 1 drop of ferric ammonium sulfate T.S. to one portion, then dilute both portions with 2 cc. of water: the solution containing the iron salt darkens in color and a reddish-brown flocculent precipitate forms; the iron-free solution yields a rose-red flocculent precipitate.

Dissolve about 25 mg. of ethinyl estradiol in 10 cc. of 5 per cent potassium hydroxide solution contained in a glass stoppered tube; add 0.1 Gm. of benzoyl chloride and shake the precipitate and recrystallize it from methanol and dry the crystals: the benzoylated product melts at 200-202°C.

Dry about 25 mg. of ethinyl estradiol, accurately weighed, for 4 hours in an Abderhalden dryer at room temperature, over phosphorus pentoxide at a pressure not exceeding 1 mm. of mercury: the loss in weight does not exceed 0.5 per cent.

Ash about 5 mg. of ethinyl estradiol, accurately weighed, in a tared platinum vessel: the residue does not exceed 0.1 per cent.

### ETHYL SALICYLATE.— $C_9H_{10}O_3$ .—M. W. 166.17.

Ethyl salicylate is a transparent, colorless, volatile liquid possessing a pleasant characteristic odor and taste. Its specific gravity is 1.132 at 20 C. and it boils at from 230 to 232 C. It is insoluble in water, but soluble in alcohol.

**ETHYLSTIBAMINE.**—A pentavalent antimony-organic complex mixture consisting of *p*-aminophenylstibonic acid, largely as a tetramer; *p*-acetylaminophenylstibonic acid, largely as a dimer; antimononic acid; and diethylamine in the approximate molar ratio of 1:2:1:3, respectively.

Ethylstibamine occurs as a light yellow to yellow-brown, odorless powder, easily soluble in water. The  $pH$  of a 5 per cent solution is not less than 6.5 nor more than 7.6.

Dissolve 0.1 Gm. of ethylstibamine in 10 cc. of 5 per cent sodium carbonate solution, and extract with 20 cc. of ether. Wash the ether solution with 10 cc. of water and extract with 10 cc. of diluted hydrochloric acid. To the acid extract add 0.1 cc. of tenth-normal sodium nitrite solution, allow to stand one minute; add two drops of 1 per cent sulfamic acid and 1 drop of 0.1 per cent naphthylethylenediamine: no more color develops than is obtained by similarly treating 0.05 mg. of aniline. Acidify the extracted sodium carbonate solution with diluted hydrochloric acid. Add 2 drops of tenth-normal sodium nitrite solution, and pour into a freshly prepared alkaline solution of "H" acid (1-amino-8-naphthol-3,6-disulfonic acid): a cherry-red color results.

Heat 0.5 Gm. of ethylstibamine dissolved in sodium carbonate T.S.: the vapor turns moist red litmus paper blue.

Saturate with hydrogen sulfide the solution remaining after the assay for total antimony: an orange colored precipitate is formed.

Acidify a solution of 0.1 Gm. of ethylstibamine in 5 cc. of water with diluted nitric acid; boil, cool and filter: 2 cc. of the filtrate shows no more *chloride* than corresponds to 1 cc. of fiftieth-normal hydrochloric acid. Another 2 cc. of the filtrate shows no more *sulfate* than corresponds to 1 cc. of fiftieth-normal sulfuric acid.

Dissolve 0.1 Gm. of ethylstibamine in 10 cc. of water, acidify with 0.1 cc. of glacial acetic acid, collect the precipitate on a small filter and

wash it three times with 5 cc. portions of water. Remove the precipitate and filter paper to a glass stoppered flask, make up to a volume of approximately 25 cc. with water, add 3 cc. of 15 per cent sodium carbonate solution and shake the mixture thoroughly. Filter the alkaline solution and wash the filter and filter paper mass with water. Combine the filtrate and washings, acidify by the addition of 24 cc. of 10 per cent tartaric acid solution and titrate with twentieth-normal iodine solution using 1 per cent starch solution as the indicator. Titrate a blank control using the same reagents. Each cc. of the twentieth-normal iodine is equivalent to 3.045 mg. of trivalent antimony. The amount of trivalent antimony found is not greater than 1.0 per cent.

Dry about 0.5 Gm. of ethylstibamine, accurately weighed, in a low-form weighing dish, at room temperature for 24 hours in a vacuum desiccator over phosphorus pentoxide at a pressure not greater than 5 mm. of mercury: the loss in weight is not more than 6.0 per cent.

To about 0.2 Gm. of ethylstibamine, accurately weighed, in a 500 cc. glass stoppered Erlenmeyer flask, add 2 Gm. of finely powdered potassium permanganate and 10 cc. of 1:8 sulfuric acid. Place on a steam bath and allow to stand 10 minutes, frequently rotating the flask to insure thorough mixing. Cautiously add 10 cc. of sulfuric acid in 2 cc. portions, rotating the flask after each addition. Place a small funnel in the neck of the flask and heat until fumes of sulfur trioxide are evolved. Cool, add 15 cc. of hydrochloric acid, boil until clear and colorless, cool, add 75 cc. of hydrochloric acid and 50 cc. of water, cool, add 2.5 Gm. of potassium iodide, stopper and allow to stand in the dark for 1 hour. Add 125 cc. of distilled water, 5 cc. of chloroform and titrate with tenth-normal sodium thiosulfate to the disappearance of the pink color in the chloroform layer. Run a blank on the reagents and make the necessary corrections. Each cc. of tenth-normal sodium thiosulfate corresponds to 6.09 mg. of antimony: the amount of antimony found corresponds to not less than 41 per cent nor more than 45 per cent calculated on the dry basis.

Place about 0.1 Gm. of ethylstibamine, accurately weighed, in a flask fitted for steam distillation; add 10 cc. of normal sodium hydroxide solution, and steam distil, collecting the distillate in 10 cc. of 2 per cent boric acid solution. Add 2 drops of methyl red-bromocresol green indicator (*Ind. Eng. Chem., Anal. Ed.*, 14: 280, 1942), and titrate with fiftieth-normal hydrochloric acid. Each cc. of fiftieth-normal hydrochloric acid is equivalent to 14.62 mg. of diethylamine: the amount of diethylamine corresponds to not less than 7.5 per cent nor more than 8.5 per cent, calculated on the dry basis.

Dissolve about 0.3 Gm. of ethylstibamine, accurately weighed, by sprinkling the powder on 10 cc. of water in a 25 cc. Erlenmeyer flask. When solution is complete add 0.1 cc. of glacial acetic acid. Transfer the precipitate to a filter and wash the flask twice with 3 cc. portions of distilled water which are passed through the filter. After the wash water has passed through the filter the precipitate and filter paper are transferred to a 250 cc. glass stoppered Erlenmeyer flask. Three cc. of 15 per cent sodium carbonate solution are added to the flask; it is closed with the glass stopper and shaken vigorously. The suspension of the material is transferred to a filter and washed with 10 cc. of water containing 2 cc. of 15 per cent sodium carbonate solution, 10 cc. of water containing 1 cc. of sodium carbonate solution and 10 cc. of water. The filtrate and washings, in a 250 cc. beaker, are acidified with 5 cc. of 1:1 hydrochloric acid and the free amine is titrated with tenth-normal sodium nitrite. Starch-cadmium iodide paper is used as an external indicator. The end point is read thirty seconds after the addition of the nitrite to the solution. The value of the amine content is calculated in terms of acetyl ( $\text{CH}_3\text{CO}-$ ): each 1 cc. of tenth-normal sodium nitrite is equivalent to 0.0043 Gm. of acetyl.

The acetylated amine content is now determined by saponifying the product and titrating the total amine. The difference between the subsequent titration and that on the unsaponified material represents, when calculated in terms of acetyl, the acetyl content of the ethylstibamine. Dissolve about 0.3 Gm. of ethylstibamine, accurately weighed, by sprinkling it on the surface of 10 cc. of water contained in a 125 cc. glass stoppered Erlenmeyer flask to which is fitted a glass joint air condenser. To the solution is added 7 cc. of 5 normal sodium hydroxide and the condenser is attached. The flask with the attached condenser is then placed in a bath of boiling water. The outside water level should be kept above the

level of the solution at all times. The heating is continued 3.5 to 4 hours. After completion of the saponification, the condenser is washed down with a little distilled water; the solution is then acidified with 5 cc. of 1:1 hydrochloric acid and transferred to a 250 cc. beaker. It is titrated with tenth-normal sodium nitrite and the value of the acetyl content obtained by difference.

The acetyl content is not less than 6.0 per cent nor more than 7.0 per cent calculated on the dry basis.

**FERROUS LACTATE.**— $C_6H_{10}FeO_6 \cdot 3H_2O$ .—M. W. 288.06.

Ferrous lactate occurs in pale greenish-white crusts, consisting of small needle-shaped crystals or transparent green scales, having a slight, peculiar odor and a sweetish, ferruginous taste. It is slowly soluble in about 40 parts of cold and in 12 parts of boiling water; almost insoluble in alcohol; and freely soluble in a solution of an alkali citrate, yielding a green solution. When strongly heated, the salt froths, gives out dense, white, acid fumes, chars and finally leaves a brownish-red residue.

The aqueous solution of the salt has a greenish-yellow color and a slightly acid reaction, and gives a deep blue precipitate with potassium ferricyanide and a light blue one with potassium ferrocyanide. A 2 per cent aqueous solution of the salt should not yield more than a faint opalescence with a lead acetate solution (*limit or absence of sulfate, chloride, citrate, tartrate and malate*). The aqueous solution after acidification with hydrochloric acid should not yield any precipitate or color when treated with hydrogen sulfide (*foreign metals*). The aqueous solution, acidified with nitric acid, should not afford more than slight opalescence with barium chloride T.S. or with silver nitrate T.S. (*limit of sulfate or chloride*). If 25 cc. of a 2 per cent aqueous solution of the salt is mixed with 5 cc. of diluted sulfuric acid, the mixture boiled for a few minutes, an excess of sodium hydroxide T.S. added and the mixture filtered. The filtrate, when mixed with a few drops of alkaline cupric tartrate solution and boiled, does not yield a red precipitate (*sugar*). If a portion of the salt is triturated with sulfuric acid, no offensive odor is developed (*butyric acid*), nor is any gas evolved (*carbonate*) and the mixture, after standing for some time, does not assume a brown color (*sugar, gum or other readily carbonizable impurities*). If from 1 to 1.5 Gm. of the salt is weighed and moistened with nitric acid and carefully ignited in a porcelain crucible it leaves a residue of ferric oxide, weighing not less than 27 per cent nor more than 27.8 per cent of the material taken: this residue does not have an alkaline reaction on litmus paper, nor yield anything soluble to water (*foreign salts*).

**FIBRIN FOAM.**—A sterile, dry preparation of fibrin prepared from Fraction I of citrated normal human plasma as fractionated by the method of Cohn (*J. Am. Chem. Soc.* 68: 459, 1946).

Fibrin foam (human) consist of small, yellowish, rectangular, fragile, sponge-like pieces which become compressible and resilient when completely wetted with water. The loss in weight on drying a specimen of fibrin foam over phosphorus pentoxide in a vacuum is not more than 5 per cent. The residue on ignition shall not exceed 8 per cent.

Peptic digestion of a 50 mg. piece of fibrin foam in 100 cc. of a 1 per cent solution of Pepsin, N.F., in tenth-normal hydrochloric acid at 37° C. should require less than 30 minutes.

Fibrin foam complies with the requirements of the National Institute of Health of the United States Public Health Service.

**FOLIC ACID.**—Pteroylglutamic acid— $N-[4-\{(2\text{-amino-4-hydroxy-6-pteridyl)methyl}\}amino\}benzoyl]\text{ glutamic acid}$ .— $C_{19}H_{19}O_6N_7$ .—M. W. 441.4.

Folic acid occurs as a yellowish-orange crystalline powder. It is insoluble in alcohol, benzene, chloroform, ether and water; very slightly

soluble in hot water; and sparingly soluble in tenth normal sodium hydroxide.

Place about 0.1 Gm. of folic acid, accurately weighed, in a dry 125 cc., glass-stoppered Erlenmeyer flask, and add 25 cc. of anhydrous methanol. Swirl the flask to break up any small lumps. Titrate the slurry by the standard Karl Fischer method (*Angew. Chem.* 48:394, 1935; *J. Am. Chem. Soc.* 61:2407, 1939), modified to add an excess of Karl Fischer reagent and back titrate with a standard alcohol-water solution. Alternatively, dry about 0.1 Gm. of folic acid, accurately weighed, in a vacuum over phosphorus pentoxide at room temperature in the dark for 120 hours. The loss in weight by either method does not exceed 10 per cent.

Char over a low flame 0.2 Gm. of folic acid, accurately weighed. Cool, then moisten the charred material with 1 cc. of sulfuric acid. Cautiously ignite until ashing is complete: the residue does not exceed 0.5 per cent on the dry basis.

Treat the residue from the sulfated ash with 2-3 drops of hydrochloric acid and evaporate to dryness on a steam bath. Add 10 cc. of 2 per cent hydrochloric acid and heat for 5 minutes on a steam bath. Filter through paper into a Nessler tube. Repeat the acid treatment of the residue with 10 cc. more of 2 per cent hydrochloric acid. Dilute the combined filtrates to 25 cc., and add 10 cc. of hydrogen sulfide T.S. Keep in the dark for 10 minutes: no more turbidity develops than corresponds to 50 p.p.m. of lead (*U. S. P. XIII*).

Place about 0.1 Gm. of *p*-aminobenzoic acid, of known purity, accurately weighed, in a 100 cc. volumetric flask, add 50 per cent alcohol to dissolve the solid, and dilute to the mark with 50 per cent alcohol. Transfer 1 cc. of the *p*-aminobenzoic acid solution to a 250 cc. volumetric flask, add 200 cc. of water, 25 cc. of five normal hydrochloric acid, 2.5 cc. of a 0.5 per cent gelatin solution (0.5 Gm. gelatin and 0.1 Gm. benzoic acid in 100 cc. of water), and finally dilute to the mark with water. Prepare a standard curve, using sufficient solution to give a range of final concentrations of 4 to 20 micrograms, e.g. measure quantities of 1, 2, 3, 4 and 5 cc., respectively, into separate 10 cc. volumetric flasks; dilute to 6.6 cc. with water, add 0.4 cc. of five normal hydrochloric acid and 1 cc. of 0.1 per cent sodium nitrite solution; mix and let stand 3 minutes, and add 1 cc. of 0.5 per cent ammonium sulfamate solution; mix and let stand 2 minutes, and add 1 cc. of a 0.1 per cent N-(1-naphthyl)ethylenediamine dihydrochloride solution; mix and allow to stand 5 minutes. Read the light absorption of the solution with a spectrophotometer at 5500 Å., using water as a blank, and plot the optical density versus concentration.

Weigh, accurately, about 0.1 Gm. of folic acid and transfer it to a 100 cc. volumetric flask. Dissolve the folic acid and dilute to the mark with tenth-normal sodium hydroxide. Transfer 1 cc. of the solution to a 100 cc. volumetric flask and add 80 cc. of water, 10 cc. of five normal hydrochloric acid, 1 cc. of 0.5 per cent gelatin solution, and water to the mark. Withdraw 10 cc. of the mixed solution before reduction and determine the free amine in terms of *p*-aminobenzoic acid by treating 2 cc. contained in a 10 cc. volumetric flask as directed for *p*-aminobenzoic acid, beginning with the phrase, "dilute to 6.6 cc. with water . . ." Transfer the rest of the solution to a 250 cc. Erlenmeyer flask and add 0.5 Gm. of zinc dust. Allow the mixture to stand 10 minutes with intermittent shaking. Filter to free the reduced solution of zinc dust. Pipette 2 cc. of the reduced solution to a 10 cc. volumetric flask and develop the color as directed for *p*-aminobenzoic acid. From the standard curve, determine the concentration of total amine in the solution in terms of *p*-aminobenzoic acid.

Calculate the folic acid present from the following equation:

$$\frac{\text{(micrograms total amine as } p\text{-aminobenzoic acid} - \text{micrograms free amine as } p\text{-aminobenzoic acid)}}{\text{folic acid found}} \times 3.22 = \text{micrograms}$$

The folic acid content is not less than 90 per cent calculated on the dry basis.

**FOLIC ACID TABLETS:** Weigh, accurately, 25 tablets of folic acid and grind them to a fine powder in a mortar. Weigh out an amount of powder equivalent to 0.1 Gm. of folic acid. Transfer the weighed portion to a 100 cc. volumetric flask and dilute to 100 cc. with tenth-normal sodium hydroxide. Centrifuge and transfer 1 cc. of the supernatant liquid to a 100 cc. volumetric flask. Continue the assay for folic acid as directed in

the monograph for folic acid, beginning with the sentence, "Transfer 1 cc. of the solution to a 100 cc. volumetric flask and add 80 cc. of water, 10 cc. of five normal hydrochloric acid . . ." The folic acid content of the tablets is not less than 90 nor more than 115 per cent.

**GASTRIC MUCIN.**—The fraction precipitated by approximately 60 per cent alcohol from the supernatant liquid after pepsin-hydrochloric acid digestion of hog stomach linings.

Gastric mucin occurs as a white to yellow powder or brownish yellow granules. It possesses a slightly salty taste and characteristic odor indicative of peptones. Both forms yield a viscous gray, opalescent solution when triturated with water.

Dry approximately 1 Gm. of gastric mucin, accurately weighed, to constant weight at 100 C.: the loss in weight does not exceed 6 per cent.

Incinerate approximately 1 Gm. of gastric mucin, accurately weighed, in a muffle furnace at 500 C.: the ash content does not exceed 6.5 per cent.

Transfer a 10 Gm. sample of gastric mucin to a 125 cc. Erlenmeyer flask and add 100 cc. of 70 per cent alcohol (737 cc. of U. S. P. alcohol diluted to 1 liter). Stopper the flask, shake the mixture for thirty minutes and decant the supernatant liquid. Repeat this addition of alcohol and extraction for a total of six times. Measure the combined extracts and filter a portion through a dry filter paper. Evaporate 50 cc. of the filtrate to dryness, dry at 100 C. and 72 cm. of mercury to constant weight, and calculate the dry weight,  $S$ , in the total volume of alcohol. The mucin content, calculated as  $(10-S) \times 10$ , is not less than 73 per cent nor more than 90 per cent.

Determine the nitrogen content in the dried alcohol insoluble residue (described in the foregoing paragraph) by the Kjeldahl method according to *Methods of Analysis of the Association of Official Agricultural Chemists*, 6, ed., p. 25: the nitrogen content is not less than 7.0 nor more than 9.0 per cent.

Transfer 0.1 Gm. of the dried alcohol insoluble residue as previously obtained to a 125 cc. Erlenmeyer flask and add 50 cc. of two-normal sulfuric acid. Digest on a steam bath under a reflux condenser for three hours and dilute to 100 cc. Transfer 4 cc. of this solution to a 25 by 200 mm. test tube, add 1 drop of phenolphthalein and neutralize with 30 per cent sodium hydroxide. Add 5 cc. of standard copper reagent [Twenty-five Gm. of anhydrous sodium carbonate, 20 Gm. of sodium bicarbonate and 25 Gm. of potassium sodium tartrate are dissolved in 600 cc. of distilled water; 7.5 Gm. of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  is dissolved in 100 cc. of water and introduced with constant stirring into the carbonate tartrate solution through a funnel resting on the bottom of the container. To the solution add 5 Gm. of potassium iodide and 22 cc. of an alkaline standard normal solution of potassium biiodate (32.498 Gm. of potassium biiodate and 83.3 cc. of normal sodium hydroxide made up to 1 liter). The resultant solution is made up to exactly 1,000 cc.] and make up to 10 cc. Cover the test tube with a small beaker and suspend it in boiling water for fifteen minutes and then cool in a pan of cold water without shaking. Add 5 cc. of normal sulfuric acid and after one minute titrate with 0.005 normal sodium thiosulfate, using starch as an indicator. The sodium thiosulfate is standardized against the 0.022 normal copper sulfate-iodate reagent, 5 cc. of which should require 22.0 cc. of the thiosulfate. The difference between this control figure and the number of cubic centimeters of thiosulfate used in the determination should not be less than 8.6 nor more than 12.2 cc., that is, not less than 25 per cent nor more than 35 per cent of reducing material, calculated as dextrose in the alcohol insoluble material.

Prepare a 2 per cent solution of gastric mucin by triturating 2 Gm. of mucin with 100 cc. of water and passing it through a 60 mesh screen. Determine the  $\text{pH}$  of this solution by means of a glass electrode at 25 C.: the  $\text{pH}$  is not below 3.7 nor above 6.5. Determine the viscosity of this solution at 25 C. within one hour by means of a 10 cc. Mohr pipet and compare it with water: the relative viscosity is not below 1.30 nor above 3.50.



**GITALIN (AMORPHOUS).**—A glycosidal constituent of *Digitalis purpurea* Linné prepared according to the method of Kraft.

Gitalin (amorphous) is a white or slightly buff colored amorphous powder which is readily soluble in chloroform, ether, acetone and alcohol and is slowly soluble in 600 parts of cold water. It is insoluble in petroleum ether and carbon disulfide. Its aqueous solution is neutral to litmus and possesses an intensely bitter taste. It has no sharp melting point but undergoes some decomposition when heated to 110° C. and becomes fluid as the temperature is raised to 150° C. When its aqueous solution is boiled, gitalin (amorphous) is converted into anhydrogitalin, with a subsequent loss of about 30 per cent in potency.

Dissolve 10 mg. of gitalin (amorphous) in 3 cc. of glacial acetic acid in a narrow test tube, and add to this one drop of 5 per cent ferric chloride solution. Underlay this solution with concentrated sulfuric acid: a brownish red zone appears at the point of contact. The upper acetic acid layer assumes a bluish-green color, gradually changing to indigo blue. Repeat the test without the addition of ferric chloride: a brown zone appears at the point of contact, and the upper acetic acid layer remains green. Concentrated sulfuric acid containing 10 mg. of gitalin (amorphous) and a trace of ferric chloride produces a brown color, gradually changing to red and finally to violet. When an aqueous solution of gitalin (amorphous) is heated for one hour at 100° C., its potency (cardiac activity) is reduced 30 per cent. This "titer-drop" is a characteristic feature of gitalin (amorphous) and is due to the conversion of gitalin into anhydrogitalin. It does not occur with digitoxin.

**GOLD SODIUM THIOMALATE.**— $C_4H_3AuNa_2O_4S$ .  $H_2O$ .—M. W. 408.33.—Disodium aurothiomalate.

Gold sodium thiomalate occurs as a fine, white to yellowish-white powder possessing a metallic taste. It is very soluble in water and practically insoluble in alcohol and in ether. Aqueous solutions of gold sodium thiomalate are colorless to pale yellow. The pH of a 5 per cent aqueous solution is between 5.8 and 6.8.

Dissolve about 50 mg. of gold sodium thiomalate in 5 cc. of water and divide the solution into four portions. To one portion add about 0.25 cc. of calcium nitrate T.S.: a white precipitate is formed, which dissolves on addition of diluted nitric acid but reprecipitates on the addition of ammonium acetate T.S. To a second portion add 1 cc. of calcium nitrate solution, mix and centrifuge. Decant the supernatant liquid and add 0.25 cc. silver nitrate T.S.: no precipitate results. To a third portion add about 0.25 cc. of silver nitrate T.S.: a yellowish precipitate is formed, which dissolves completely on the addition of an excess of strong ammonia solution. To the fourth portion in a porcelain dish add about 0.25 cc. of strong ammonia solution and 0.25 cc. of 30 per cent hydrogen peroxide, evaporate and ignite. Add 5 cc. of water to the residue and filter the mixture: particles of gold are found on the filter and the filtrate responds to tests for sodium and sulfate.

Dry about 0.5 Gm. of gold sodium thiomalate, accurately weighed, at room temperature, in a desiccator over fresh phosphorus pentoxide for 24 hours: the loss in weight does not exceed 6.0 per cent.

Weigh accurately about 0.5 Gm. of gold sodium thiomalate and transfer it to a 300 cc. Kjeldahl flask with about 10 cc. of water, add 20 cc. of nitric acid and mix well. Add 15 cc. of sulfuric acid slowly with mixing and heat over a low flame, at first gently boiling and later increasing the heat until fumes of sulfur trioxide are evolved. Allow the flask and contents to cool to room temperature and add 30 cc. of water slowly with mixing. The precipitated gold should agglomerate and the liquid should not have a purplish color (*colloidal gold*). If the liquid is not colorless, add 20 cc. of 3 per cent hydrogen peroxide, reheat as directed, recool and redilute. Filter through an ignited tared Gooch crucible, wash with water, dry at 100° C., ignite, cool and weigh: the weight of gold found corresponds to not less than 49.5 per cent nor more than 50.7 per cent, calculated to the dried substance.

**HEPARIN SODIUM.**—The hydrated sodium salt of a naturally occurring, complex organic polymer possessing anti-coagulant properties. The chemical structure of heparin has not been fully established. It is considered to be a dextrorotatory polysaccharide made up of hexosamine and hexuronic acid units containing sulfuric acid ester groups.

Heparin sodium occurs as a white to lightly colored, amorphous, gumlike powder. It is very soluble in water but practically insoluble in alcohol, acetone, benzene, chloroform and ether. The pH of a 1 per cent solution of heparin sodium lies in the range 6 to 7 at 25 C.

Place 5 cc. of 0.005 per cent toluidine blue O solution (made by dissolving 25 mg. of toluidine blue O in 500 cc. of water containing 1 cc. of diluted hydrochloric acid) in a test tube, add 5 cc. of water and 1 cc. of 1 per cent heparin sodium solution; the color of the mixture changes from blue to reddish blue; add 2 cc. of petroleum ether and shake the mixture vigorously for one minute. Allow the emulsion to break: the color of the solution returns to pale blue and a purple precipitate collects in the interface between the liquids.

Place 1 cc. of 1 per cent heparin sodium in a test tube; add 2.5 cc. of ortho-phenanthroline T.S.: a red precipitate forms.

Fuse about 50 mg. of heparin sodium with a small piece (2 mm.) of metallic sodium in a test tube; cool, add 5 drops of alcohol, leach the fused mass with 5 cc. of water and filter: the filtrate responds to tests for cyanide and sulfide, indicating the presence of nitrogen and sulfur respectively.

Add 1 drop of strong ammonia solution and 3 drops of 30 per cent hydrogen peroxide solution to 0.5 cc. of 1 per cent heparin sodium solution contained in a test tube. Heat on a water (steam) bath for ten minutes: no cloudiness results which cannot be cleared by making the solution acid to congo red, by the addition of just sufficient diluted hydrochloric acid (*barium ion*).

Mix 5 cc. of 1 per cent heparin sodium solution with 5 cc. of sulfosalicylic acid reagent (dissolve 20 Gm. of sodium sulfate decahydrate in 80 cc. of water, cool to 35 C., add 5.0 Gm. of sulfosalicylic acid, dissolve and dilute to 100 cc.). Heat the mixture to boiling: no cloudiness should be discernible (*protein*).

Ash 0.1 Gm. of heparin sodium in the presence of sulfuric acid in a tared porcelain crucible: the sulfated ash amounts to not more than 40.5 per cent of the dried substance.

Dry about 0.1 Gm. of heparin sodium for twenty-four hours at room temperature over phosphorus pentoxide in a vacuum desiccator at a pressure not above 5 mm. of mercury: the loss in weight is not more than 12 per cent.

Heparin sodium shall meet the pyrogen test described in the U. S. P. *XIII* when solutions containing 1,000 units per cubic centimeter are injected in a dosage of 2.0 cc. per kilogram of body weight.

**HEXESTROL.**— $C_{18}H_{22}O_2$ .—M. W. 270.36.—*Meso*-3,4-di-*para*-hydroxyphenyl-n-hexane.

Hexestrol occurs as an odorless white crystalline powder which melts at 185-188° C. It is freely soluble in ether; soluble in acetone, alcohol and methanol; slightly soluble in benzene and chloroform; and practically insoluble in water and in dilute mineral acids. It may be dissolved in vegetable oils and in dilute solutions of sodium or potassium hydroxide. When recrystallized from diluted alcohol, hexestrol appears in the form of thin, platelike crystals of irregular, serrated outline.

Dissolve about 10 mg. of hexestrol in 10 cc. of diluted alcohol and add three drops of 1 per cent ferric chloride T.S.: a yellowish green color develops which changes to yellow. Add a few drops of 50 per cent solution of antimony pentachloride in dry alcohol free chloroform to a very dilute solution of hexestrol in the same solvent: a red colored solution is produced. Dissolve 10 mg. of hexestrol in 5 cc. of concentrated sulfuric acid: no color is produced (*distinction from diethylstilbestrol, which yields an orange color*).

The hexestrol diacetate obtained in the assay given below melts at 137-139° C.

Dry an accurately weighed specimen of hexestrol to constant weight at 100 C.: the loss does not exceed 0.5 per cent. Ignite an accurately weighed specimen of hexestrol: the residue is not more than 0.05 per cent. Dissolve 0.1 Gm. of hexestrol in 10 cc. of warm sodium hydroxide T.S.: the solution is clear and colorless; dilute to 20 cc. with distilled water and add 5 drops of 10 per cent sodium sulfide solution: the darkening produced does not exceed that of a control to which has been added 0.02 mg. of lead.

Transfer to a suitable flask about 0.5 Gm. of dried hexestrol, accurately weighed, and add 2 cc. of acetic anhydride and 4 cc. of dry pyridine. Boil the mixture under a reflux condenser for fifteen minutes; cool, add 50-60 cc. of distilled water and shake the flask and contents thoroughly. Stopper the flask and place it in the cold for one to one and one-half hours. Collect the precipitate on a suitable filter and wash it with four 20 cc. portions of distilled water. Dry the precipitate at 75-80° C. overnight, cool and weigh: the weight of the dry hexestrol diacetate obtained, when multiplied by 0.7628, corresponds to a hexestrol content of not less than 98.5 per cent and not more than 100.5 per cent.

**HEXETHAL SODIUM.** —  $C_{12}H_{19}N_2NaO_3$ . — M. W. 262.29.—The monosodium salt of 5-*n*-hexyl-5-ethyl barbituric acid.

**Caution:** Aqueous solutions of hexethal sodium are not stable but decompose on standing; on boiling, precipitation occurs with evolution of ammonia.

Hexethal sodium is an odorless, white or slightly yellowish powder, with a bitter taste. It is very soluble in water; soluble in alcohol and practically insoluble in ether and benzene. An aqueous solution of hexethal sodium has an alkaline reaction to litmus.

Dissolve about 0.5 Gm. of hexethal sodium in 100 cc. of water, add an excess of diluted hydrochloric acid, collect the resultant hexylethyl barbituric acid on a filter, wash and dry at 90 C.: it melts at 122-125 C. Incinerate about 1 Gm. of hexethal sodium: the residue responds to tests for sodium carbonate. Boil about 0.5 Gm. of hexethal sodium with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with evolution of ammonia. Dissolve about 0.3 Gm. of hexethal sodium in 10 cc. of water and divide into two portions; to one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in an excess of strong ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in an excess of strong ammonia solution.

Dissolve about 0.5 Gm. of hexethal sodium in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper: separate portions of 10 cc. each of the filtrate yield no greater opalescence on the addition of 1 cc. of silver nitrate T.S. than that produced by 0.25 cc. of tenth-normal hydrochloric acid in 50 cc. of water (*chloride*); no turbidity on the addition of 1 cc. of barium nitrate T.S. (*sulfate*). To about 0.2 Gm. of hexethal sodium in 25 cc. of water, add 1 cc. of diluted hydrochloric acid, filter through paper: the filtrate yields no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*). Add about 0.1 Gm. of hexethal sodium to 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substance*).

Transfer about 1 Gm. of hexethal sodium, accurately weighed, to a glass stoppered cylinder, add 50 cc. of anhydrous ether, stopper and shake for ten minutes; decant the supernatant liquid through filter paper and repeat twice, using 25 cc. and 15 cc. portions, respectively, of ether, utilizing the same filter; evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 90 C.: the residue does not exceed 0.5 per cent (*uncombined hexylethyl barbituric acid*).

Dry about 1 Gm. of hexethal sodium, accurately weighed, to constant weight at 100 C.: the loss does not exceed 2.5 per cent. Transfer about 0.5 Gm. of hexethal sodium, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by 10 cc. of diluted hydrochloric acid; extract with eight successive portions of ether of 25 cc.

each, evaporate the combined ethereal extracts to dryness in a stream of warm air and dry to constant weight at 90° C.: the amount of hexylethyl barbituric acid corresponds to not less than 90.8 per cent nor more than 91.6 per cent calculated to the dried substance. Transfer the acidified aqueous portion from the foregoing extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained add 5 cc. of sulfuric acid; heat *cautiously* until the excess of sulfuric acid has been volatilized; repeat twice, using 1 cc. portions of sulfuric acid each time; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 8.5 per cent, nor more than 9 per cent when calculated to the dried substance.

**HEXOBARBITAL SOLUBLE.**— $C_{12}H_{15}N_2NaO_3$ .—M. W. 258.25.—The monosodium salt of 1,5-dimethyl-5- $\Delta^1$ -cyclohexenyl barbituric acid.

Hexobarbital soluble occurs as a white, crystalline, odorless, hygroscopic powder, with a slightly bitter taste. It is very soluble in water, freely soluble in alcohol, and practically insoluble in ether. An aqueous solution of hexobarbital soluble is alkaline to litmus. The  $pH$  of a 10 per cent solution of hexobarbital soluble lies between 11 and 12.

Dissolve about 0.5 Gm. of hexobarbital soluble in 100 cc. of water, add an excess of diluted hydrochloric acid, mix, allow to stand fifteen minutes and collect the resultant cyclohexenyldimethyl barbituric acid on a filter, wash with water and dry at 65° C.: it melts at 143-146° C.

Transfer about 0.1 Gm. of the dried cyclohexenyldimethyl barbituric acid to a stoppered cylinder, add 25 cc. of water, shake the mixture for one minute, filter through paper and divide into two portions: to one portion add 1 cc. of 36 per cent acetic acid and 0.5 cc. of bromine T.S.: an immediate discoloration occurs; to the other portion add 0.1 cc. of potassium permanganate T.S.: a pale brownish-yellow color appears.

Transfer about 0.5 Gm. of hexobarbital soluble to a 50 cc. Erlenmeyer flask, add 5 cc. of water and about 0.4 Gm. of *p*-nitrobenzyl chloride dissolved in 10 cc. of 90 per cent alcohol. Attach the flask to a reflux condenser and heat the mixture on a water bath for one-half hour. Cool the flask and collect the precipitate on a filter, wash with water, dry at 65° C., dissolve the dry product in just sufficient hot 60 per cent alcohol, cool and collect the precipitate; dry at 65° C.: the melting point of the product is 113-115° C.

Transfer about 0.3 Gm. of hexobarbital soluble to a test tube containing 2 cc. of water and add, dropwise, bromine T.S. until the color of bromine faintly persists after vigorously shaking the test tube. Pour the contents of the test tube into 100 cc. of water, filter through paper, wash with water and dry at 65° C.: the melting point of the product lies between 130° and 132° C., with decomposition.

Incinerate about 1 Gm. of hexobarbital soluble in a porcelain dish, cool, dissolve the residue in 50 cc. of water and divide into two portions: the first portion responds to tests for sodium carbonate. Rinse the porcelain dish with 2 cc. of diluted hydrochloric acid, add the rinsings to the second portion and filter through paper: the filtrate yields no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Boil about 0.5 Gm. of hexobarbital soluble with 5 cc. of a 25 per cent sodium hydroxide solution: it is decomposed with evolution of ammonia.

Dissolve about 0.5 Gm. of hexobarbital soluble in 10 cc. of water and divide the solution into two portions; to one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, insoluble in excess water, partially soluble in an excess of strong ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble both in excess water and in an excess of strong ammonia solution.

Dissolve about 0.5 Gm. of hexobarbital soluble in 50 cc. of water, add 5 cc. of diluted nitric acid, allow to stand for fifteen minutes and filter through paper: separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate T.S. (*chloride*); no turbidity on the addition of 1 cc. of barium nitrate T.S. (*sulfate*).

Add about 0.1 Gm. of hexobarbital soluble to 2 cc. of sulfuric acid: the solution is pale yellow, gradually changing to brownish orange (*easily carbonizable substances*). Dry about 1 Gm. of hexobarbital soluble, accurately weighed, to constant weight at 65° C.: the loss in weight is negligible.

Transfer about 0.5 Gm., accurately weighed, of the dried hexobarbital soluble to a tared porcelain dish, add 2 cc. of sulfuric acid, cautiously ignite until the excess of sulfuric acid has been volatilized, repeat the ignition twice with the addition of 1 cc. of sulfuric acid; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 8.5 nor more than 9.4 when calculated to the dried substance.

Transfer about 0.5 Gm. of hexobarbital soluble, accurately weighed, to a suitable separator, add 15 cc. of water, followed by the addition of 10 cc. of diluted hydrochloric acid; extract the mixture with eight successive portions of chloroform using 25 cc., 15 cc. and six portions of 10 cc., respectively, evaporate the combined chloroform extracts in a tared beaker to dryness in a stream of warm air and dry to constant weight at 65° C.: the amount of cyclohexenyldimethyl barbituric acid corresponds to not less than 91 per cent nor more than 92 per cent, calculated to the dried substance.

Transfer about 0.25 Gm. of hexobarbital soluble, which has been accurately weighed in a tared stoppered weighing bottle, to a glass stoppered Erlenmeyer flask with about 20 cc. of water. Add 50 cc. of tenth-normal bromide-bromate solution and 10 cc. of hydrochloric acid; cool in ice with an occasional swirling for twenty minutes. Then add 10 cc. of 10 per cent potassium iodide solution (iodate-free) and allow to stand for ten minutes. Titrate the free iodine with tenth-normal sodium thiosulfate solution. When the titration is nearly complete, add 5 cc. of chloroform, using starch T.S. as the indicator, and continue the titration until colorless. Each cc. of tenth-normal bromide-bromate solution is equivalent to 0.0129 Gm. of hexobarbital soluble: the amount found corresponds to not less than 99 per cent nor more than 101 per cent.

### HIPPURAN-Mallinckrodt.— $C_9H_7INNaO_3 \cdot 2H_2O$ .—M. W. 363.1.—Sodium *o*-iodohippurate.

Hippuran occurs as a white, crystalline powder, possessing a faint odor and an alkaline taste. It is very soluble in water, freely soluble in alcohol and soluble in dilute alkali. An aqueous solution is neutral or faintly alkaline to litmus.

Fuse about 0.2 Gm. of Hippuran with 2 Gm. of powdered sodium hydroxide: it decomposes with the evolution of iodine vapors and ammonia. Dissolve about 0.5 Gm. of Hippuran in 100 cc. of water, add an excess of diluted hydrochloric acid; collect the resultant *o*-iodohippuric acid on a filter, wash and dry at 110° C.: it melts at 171 to 174° C. To 1 cc. of the foregoing filtrate add 10 cc. of cobalt uranyl acetate T.S.: a yellow precipitate results. Transfer about 0.5 Gm. of Hippuran to a glass-stoppered cylinder, add 25 cc. of dilute nitric acid (one part diluted nitric acid and 5 parts water), shake for five minutes, filter: the filtrate yields no distinct opalescence on the addition of 2 cc. silver nitrate T.S. (*absence of inorganic halides*).

Dissolve about 0.5 Gm. of Hippuran in 50 cc. of water, add 5 cc. diluted hydrochloric acid, filter: separate portions of 10 cc. each of the filtrate yield no turbidity on the addition of 1 cc. of barium chloride T.S. (*sulfate*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 1 Gm. of Hippuran, accurately weighed, to constant weight at 100 C.: the loss in weight is not more than 10 per cent nor less than 6 per cent. Boil about 1 Gm. of Hippuran, accurately weighed, with 10 cc. of benzene for fifteen minutes, replacing the evaporated liquid if necessary, decant the supernatant liquid through filter paper and wash the filter with 10 cc. and 5 cc. portions, of benzene; evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 100° C.: the residue does not exceed 0.2 per cent (*uncombined o-iodohippuric acid*). Transfer about 0.5 Gm. of Hippuran, accurately

weighed, to a 500 cc. Kjeldahl flask; determine the nitrogen content according to the official method described in the *Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, p. 27, paragraph 25: the percentage of nitrogen corresponds to not less than 4.1 per cent, nor more than 4.4 per cent when calculated to the dried substance. Weigh accurately about 1 Gm. of Hippuran in a tared platinum dish, add 5 cc. of sulfuric acid, heat *cautiously* while fumes of iodine and sulfur trioxide are evolved; repeat twice, using portions of 1 cc. each of sulfuric acid; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight, and weigh as sodium sulfate: the sodium found corresponds to not less than 6.8 per cent nor more than 7.3 per cent, when calculated to the dried substance. Transfer about 0.5 Gm. of Hippuran to a Parr sulfur bomb; determine the iodine content by the Lemp-Broderson method (*J. Am. Chem. Soc.* 39 : 2069): the amount of iodine found corresponds to not less than 38.5 per cent nor more than 39 per cent, when calculated to the dried substance.

**HOMATROPINE HYDROCHLORIDE.**— $C_{16}H_{21}NO_3$ . HCl.—M. W. 311.80.—The hydrochloride of the alkaloid homatropine, obtained by the condensation of tropine and mandelic acid.

Homatropine hydrochloride occurs as small white crystals, soluble in water and alcohol and melting at from 216 to 217° C.

The color test for the identification of homatropine hydrochloride and the tests showing the absence of impurities should agree with those described in the U. S. Pharmacopeia under homatropine hydrobromide.

**INVERT SUGAR SOLUTION.**—A solution of a mixture of dextrose and levulose obtained by the inversion of sucrose.

Invert sugar solution is prepared by inverting cane sugar with tartaric acid and adjusting to a pH of 6.8 with sodium hydroxide.

Invert sugar solution is a clear, pale amber, sweet, watery solution, A 10 cc. portion requires less than 2 cc. of tenth-normal sodium hydroxide to neutralize the acid, phenolphthalein T.S. being used as an indicator. No sediment separates from the solution in ampules on prolonged standing (*insoluble salts, ultramarine or prussian blue*). A 10 per cent solution is not affected by the addition of an equal volume of hydrogen sulfide T.S. (*heavy metals*). Ten cc. portions of a 10 per cent solution remain clear for at least one minute after the addition of 1 cc. of silver nitrate T.S. (*chloride*) or of ammonium oxalate T.S. (*calcium*). A portion equivalent to 5 Gm. of invert sugar shows no more sulfate than corresponds to 0.3 cc. of fiftieth-normal sulfuric acid. A solution equivalent to 5 Gm. of invert sugar evaporated to dryness and ashed yields a residue weighing not more than 4 mg. A solution equivalent to 5 Gm. of invert sugar yields not more ammonia than is equivalent to 0.5 cc. of hundredth-normal hydrochloric acid. A solution containing 16 per cent of invert sugar calculated from its copper reducing power, when examined by means of the polariscope has a specific rotation of  $[\alpha]_D^{25}$  between -16 and -18.5.

Dilute exactly 10 cc. of the original to exactly 500 cc.; transfer 10 cc. of this solution to a 250 cc. beaker and assay for invert sugar according to the *Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, pp. 571-572, paragraphs 38 and 39: the amount of invert sugar is within 5 per cent of the amount claimed. Transfer 50 cc. of the prepared solution to a 100 cc. standard flask; invert according to the *Method of Analysis, A. O. A. C.*, ed. 6, p. 566, paragraph 24c and assay for sucrose according to paragraph 30, page 569: the weight of sucrose is not greater than 4 per cent of the weight of invert sugar found.

**IOCAMFEN-Schering & Glatz.**—A liquid obtained by the interaction of iodine 10 parts, phenol 20 parts and camphor 70 parts, containing about 7.25 per cent free iodine.

Iocamfen is a dark, reddish-brown, viscid liquid, having a camphoraceous odor. It is insoluble in water, but soluble in all proportions in alcohol, ether, benzine and liquid petrolatum.

Iocamfen, like free iodine, interacts with fats and waxes, its free iodine entering into combination.

Accurately weigh about 2 Gm. of Iocamfen into a glass-stoppered flask and dissolve it in about 25 cc. of chloroform. Add about 10 cc. of potassium iodide solution (1 in 10) and titrate the free iodine with tenth-normal sodium thiosulfate solution using starch T.S. as an indicator.

**IODINATED CASTOR OIL.**—A 66 per cent solution in oil of an iodine addition product of castor oil. Iodinated castor oil contains about 17 per cent of iodine.

Iodinated castor oil is an oil-like liquid, light amber in color, having a faint alkaline reaction. It is insoluble in water; soluble in alcohol, chloroform and ether.

When heated, it is decomposed and purple vapors of iodine are given off. When heated with alcoholic potash, iodinated castor oil is saponified and potassium iodide formed.

**IDOALPHIONIC ACID.**— $C_{15}H_{12}I_2O_3$ .—M. W. 494.1.  
— $\beta$ -(4-Hydroxy-3,5-diiodophenyl)- $\alpha$ -phenyl propionic acid.

Iodoalphionic acid occurs as a white or faintly yellowish, practically odorless and tasteless powder. It is soluble in alcohol and ether, slightly soluble in benzene and chloroform, soluble in both alkali carbonate and hydroxide solutions and insoluble in water. Iodoalphionic acid melts at 157 to 162 C., with decomposition.

Shake about 0.2 Gm. of iodoalphionic acid with 2 cc. of water and 2 cc. of chloroform: the chloroform layer remains colorless (*absence of free iodine*).

Place about 0.3 Gm. of iodoalphionic acid in a 50 cc. glass stoppered cylinder, add 30 cc. of water, shake the contents for five minutes, filter through paper: separate portions of 10 cc. each of the filtrate yield a very faint opalescence with 0.5 cc. diluted nitric acid and 0.5 cc. silver nitrate solution (*soluble halides*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 0.5 Gm. of iodoalphionic acid, accurately weighed, to constant weight over sulfuric acid: the loss in weight should not exceed 0.1 per cent. Incinerate 0.5 Gm. of iodoalphionic acid, accurately weighed, in a platinum crucible: the residue does not exceed 0.1 per cent. Transfer about 0.25 Gm. of iodoalphionic acid to a bomb tube; determine the iodine content by the Carius method: the amount of iodine found corresponds to not less than 50 per cent nor more than 52 per cent, when calculated to the dried substance.

**IODOBISMUTHITE SODIUM.**— $BiI_5Na_2 \cdot 6H_2O$ .—M. W. 998.59.—Bismuth sodium iodide hexahydrate.

Iodobismuthite sodium occurs as a red crystalline compound, odorless, or having only a faint acetic or ethyl acetate odor, permanent in dry air and possessing an astringent taste. It yields a clear solution with one part water; on moderate dilution of the solution, sodium iodobismuthite hydrolyzes to form a black precipitate of bismuth iodide in a finely divided state, while on further addition of water the black precipitate changes to red bismuth oxyiodide. Hydrolysis may be retarded by the addition of acids or alkali iodides. The aqueous solution is neutral or faintly acid to litmus. Iodobismuthite sodium dissolves readily and without decomposition in ethyleneglycol, propylene glycol, glycerin, anhydrous alcohol and ethyl acetate; it is insoluble in absolute ether, chloroform, carbon disulfide, petroleum

ether, fixed oils and liquid petrolatum. On heating the product in an oven at 80 to 110 C., it loses water of hydration, with slight decomposition, leaving a maroon colored residue that becomes brown or black on aging, and that changes to red on exposure to moisture.

Add 3 cc. of hydrochloric acid and 25 cc. of water to about 0.5 Gm. of iodobismuthite sodium, add an excess of strong ammonia solution, filter and wash the filter with water. Ignite the filter in a quartz crucible; the residue is yellow. A few drops of the filtrate imparts an intense yellow color to a nonluminous flame. Add 3 cc. of ferric chloride T.S. to a 10 cc. portion of the filtrate acidified with hydrochloric acid, shake with 3 cc. of chloroform; a violet color is imparted to the chloroform. Add 5 cc. of chloroform to about 0.2 Gm. of iodobismuthite sodium and shake the mixture; the chloroform remains clear and colorless (*free iodine and distinction from quinine bismuth iodide*). Percolate 0.1 Gm. of iodobismuthite sodium with 10 cc. of absolute ether; no residue remains after the evaporation of the solvent. Add 2 cc. of nitric acid to 1.5 Gm. of iodobismuthite sodium in a quartz dish, evaporate on a steam bath and ignite at red heat; dissolve in 5 cc. of hydrochloric acid; the solution meets the requirements of the U. S. P. test for arsenic. Add just sufficient nitric acid to blacken 3 Gm. of sodium iodobismuthite contained in a 150 cc. beaker, add 100 cc. of water and boil; filter and evaporate the filtrate to 30 cc., filter again and divide the latter filtrate into portions of 5 cc. each. Mix one portion with an equal volume of dilute sulfuric acid; the liquid does not become cloudy (*lead*). Precipitate another portion with a slight excess of strong ammonia; the supernatant liquid does not exhibit a bluish tint (*copper*). Another portion is not immediately affected by barium nitrate T.S. (*sulfate*). To another portion, add diluted hydrochloric acid; no precipitate is formed (*silver*).

Transfer about 0.4 Gm. of iodobismuthite sodium, accurately weighed, to a wide mouth weighing bottle and heat to constant weight in an oven at 110 C.; the loss in weight is not less than 10.5 per cent nor more than 12.5 per cent.

Transfer about 0.2 Gm. of iodobismuthite sodium, accurately weighed, to a beaker, dissolve in 3 cc. of hydrochloric acid and 125 cc. of water, saturate the solution with hydrogen sulfide to precipitate completely the bismuth as bismuth sulfide, filter in a Gooch crucible, wash with water, alcohol, chloroform, and ether in this order, dry for one hour at 100 C., cool in a desiccator and weigh; repeat the washing with chloroform and ether and the drying at 100° C. until constant weight is attained; the bismuth sulfide is equivalent to not more than 21.8 per cent, nor less than 20.3 per cent bismuth.

Transfer about 0.2 Gm. of iodobismuthite sodium, accurately weighed, to a 250 cc. beaker, add 10 cc. of a solution of acid silver nitrate (prepared by dissolving 1 Gm. of silver nitrate in 20 cc. of water and adding 5 cc. of nitric acid) and then 100 cc. of water, allow to stand two hours, filter, using a filter paper, and wash well with water. Without allowing the precipitate to dry, puncture the filter and, using 100 cc. strong ammonia solution, wash the precipitate into a 250 cc. glass-stoppered Erlenmeyer flask, agitate the solution, then allow the flask and contents to stand two hours, collect the precipitate on a prepared Gooch crucible and wash it with diluted ammonia solution, then with water; dry to constant weight at 100° C. The weight of silver iodide is equivalent to not less than 60 per cent nor more than 63 per cent of iodine. Add 10 cc. of potassium iodide T.S. to the filtrate and heat on the steam bath until most of the ammonia has been removed, filter the solution and collect the precipitate on a prepared Gooch crucible, wash with water, dry to constant weight at 100° C.; the weight of silver iodide is equivalent to not more than 0.7 per cent chloride.

**IODOBISMUTHITE SODIUM WITH ETHYL-AMINOBENZOATE.**— $\text{BiNa}_2\text{I}_5$ .—M. W. 889.59.—A solution of sodium iodobismuthite (bismuth sodium iodide) and sodium iodide in propylene glycol containing ethyl aminobenzoate.

The specific gravity of iodobismuthite sodium with ethyl aminobenzoate at 25 C. ranges from 1.167 to 1.175. The  $\text{pH}$  of iodobismuthite



sodium with ethyl aminobenzoate taken with a quinhydrone electrode ranges from 4.5 to 5.0. The refractive index at 25 C. ranges from 1.4609 to 1.4611.

Transfer about 3 cc. of iodobismuthite sodium with ethyl aminobenzoate, accurately weighed, to an Erlenmeyer flask; add 3 cc. of hydrochloric acid and 125 cc. of water; determine the bismuth according to the method outlined under iodobismuthite sodium; each cubic centimeter contains the equivalent of not less than 0.012 nor more than 0.0138 Gm. of bismuth. Add 10 cc. of a nitric acid-silver nitrate solution (prepared by dissolving 1 Gm. of silver nitrate in 20 cc. of water and adding 5 cc. of nitric acid) to about 3 cc. of iodobismuthite sodium with ethyl aminobenzoate, accurately weighed, and then add 100 cc. of water, allow to stand two hours, filter into a prepared Gooch crucible, and wash with very dilute nitric acid (5 cc. of diluted nitric acid to make 100 cc.), and dry to constant weight at 100° C.: the weight of silver iodide is equivalent to not less than 0.135 nor more than 0.145 Gm. of iodine per cubic centimeter.

**IODOBISMUTHITE SODIUM:** The iodobismuthite sodium in iodobismuthite sodium with ethyl aminobenzoate conforms to the New and Nonofficial Remedies standards for this substance.

**ETHYL AMINOBENZOATE:** The ethyl aminobenzoate in iodobismuthite sodium with ethyl aminobenzoate conforms to the U. S. P. standards for this substance.

**PROPYLENE GLYCOL:** The propylene glycol in iodobismuthite sodium with ethyl aminobenzoate conforms to the National Formulary standards for this substance.

**IODOBASSID.**— $C_{22}H_{42}I_2O_2$ .—M. W. 592.4.—Ethyl diiodobrassidate.

Iodobrassid crystallizes in white, odorless and tasteless needles, melting at 37 C. It is insoluble in water, slightly soluble in alcohol, and very soluble in fatty oils, ether and benzene. Iodobrassid is decomposed by exposure to direct light.

The iodine content of iodobrassid is from 40.5 per cent to 41.5 per cent.

**IODOPYRACET COMPOUND SOLUTION.**—An aqueous solution containing approximately 40.5 per cent (W/V) of the dithanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid ( $C_7H_5I_2NO_3 \cdot C_4H_{11}NO_2$ .—M. W. 500.09) and approximately 9.5 per cent (W/V) of the diethylamine salt of 3,5-diiodo-4-pyridone-N-acetic acid ( $C_7H_5I_2NO_3 \cdot C_4H_{11}N$ .—M. W. 478.09).

Iodopyracet compound solution occurs as a clear, pale yellow, odorless liquid, possessing a bitter taste. It is neutral to litmus and is incompatible with mineral acids and heavy metal salts. Its specific gravity is about 1.270 at 25 C.

Dilute about 0.5 cc. of iodopyracet compound solution to 5 cc. with water and acidify with hydrochloric acid, collect the precipitate on a filter, wash with cold water and dry at 100 C.: the 3,5-diiodo-4-pyridone-N-acetic acid obtained melts at 245-249 C., with decomposition (the melting point bath previously heated to 200 C.).

Dilute about 10 cc. of iodopyracet compound solution with 20 cc. of water, acidify with hydrochloric acid and filter off the precipitate. To the filtrate add 5 cc. of approximately 50% sodium hydroxide solution and distill into about 25 cc. of normal hydrochloric acid. Evaporate the solution containing the distillate to dryness on a water bath; take up the residue in alcohol; add diethyl ether a little at a time to force out a crystalline precipitate; filter; dry the product under partial vacuum: the melting point of the diethylamine hydrochloride obtained is from 224° to 227° C., with sublimation.

Acidify the alkaline residue remaining in the distilling flask with diluted hydrochloric acid; remove the solution from the flask and evaporate to about one third of its volume. Cool the concentrated solution in ice water for fifteen minutes with occasional shaking, filter and concentrate the filtrate to a syrup. Treat the syrupy residue

with 5 cc. of absolute alcohol, neutralize by dropwise addition of sodium hydroxide T.S., filter, wash and finally dilute the filtrate to about 8 cc. with alcohol. Add about 0.5 Gm. of picric acid to the solution, boil, cool and place in an ice chest. Collect the precipitate on a filter, recrystallize from absolute alcohol and dry under partial vacuum: the melting point (*Caution!*) of the diethanolamine picrate obtained is between 109 and 110 C.

Dilute 20 cc. of iodopyracet compound solution, accurately measured, to 200 cc. in a calibrated flask. Use portions of the diluted solution in the following determinations:

Evaporate 20 cc. of the diluted solution, accurately measured, in a tared platinum dish on a water bath and dry to constant weight at 100 C.: the weight of the residue is equivalent to not less than 48 per cent (W/V) nor more than 51 per cent (W/V) calculated to the original solution. Ash the residue in the presence of sulfuric acid: the weight of the ash obtained is equivalent to not more than 0.1 per cent.

Transfer 20 cc. of the diluted solution to an ammonia distillation apparatus, add 50 cc. of water, 5 cc. of 50 per cent sodium hydroxide and distil into 30 cc. of fiftieth-normal hydrochloric acid. Titrate the excess acid with fiftieth-normal sodium hydroxide using methyl red T.S. as the indicator: the amount of fiftieth-normal hydrochloric acid consumed by the distillate is equivalent to a diethylamine content of not less than 1.4 per cent (W/V) and not more than 1.7 per cent (W/V) calculated to the original solution.

Acidify the residue remaining in the Kjeldahl flask used in the foregoing determination with sulfuric acid. Concentrate the mixture and digest with 10 cc. of sulfuric acid and 0.05 Gm. of selenium metal until clear. Cool, dilute with 100 cc. of water, transfer to the ammonia distillation apparatus and add an excess of 50 per cent sodium hydroxide. Distil into 50 cc. of tenth-normal hydrochloric acid and titrate the excess acid with tenth-normal sodium hydroxide, using methyl red T.S. as the indicator: the amount of tenth-normal hydrochloric acid consumed by the distillate is equivalent to the ammonia derived from both the 3,5-diiodo-4-pyridone-N-acetic acid and the diethanolamine.

Transfer a 10 cc. portion of the diluted solution to a 50 cc. beaker, heat gently to boiling and add exactly 12 cc. of silver nitrate T.S. Stir until the precipitate becomes granular, cool in ice water for thirty minutes with occasional stirring; filter through a tared Gooch crucible, using the cold filtrate to wash the beaker, and wash the precipitate with 5 cc. of ice cold water; dry to constant weight at 110° C. To the weight of the precipitate (silver salt of 3,5-di-iodo-4-pyridone-N-acetic acid) found, add 0.00135 Gm. as a solubility correction: the weight of silver 3,5-diiodo-4-pyridone acetate found is equivalent to a content of 3,5-diiodo-4-pyridone-N-acetic acid of not less than 40 per cent (W/V) nor more than 41 per cent (W/V) calculated to the original solution.

From the amount of 3,5-diiodo-4-pyridone-N-acetic acid found, calculate the equivalent in cc. of tenth-normal hydrochloric acid for 2 cc. of the original solution. Deduct this number of cc. of tenth-normal hydrochloric acid from the number used in the titration of the total ammonia from the Kjeldahl determination. The difference calculated as diethanolamine should be not less than 8.2 per cent (W/V) nor more than 8.7 per cent (W/V).

#### IODOPYRACET CONCENTRATED SOLUTION.—

An aqueous solution containing approximately 70 per cent of the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid ( $C_7H_5I_2NO_3 \cdot C_4H_{11}NO_2$ —M. W. 500.09).

See the tests given in the U. S. Pharmacopeia under Iodopyracet Injection, which has about half the strength of iodopyracet concentrated solution, so that the quantities given in the Pharmacopeia must be multiplied by two. See also, so far as they apply, the tests given under iodopyracet compound solution-N. N. R.

**ISOBORNYL THIOCYANOACETATE-TECHNICAL.**

— $C_{13}H_{19}N_2OS$ .—M. W. 253.35.—The technical grade of isobornyl thiocyanacetate contains 82 per cent or more of isobornyl thiocyanacetate with other terpenes.

Isobornyl thiocyanacetate-technical occurs as a yellow, oily liquid, possessing a terpene-like odor. It is very soluble in alcohol, benzene, chloroform, and ether, and practically insoluble in water. The refractive index of isobornyl thiocyanacetate-technical is 1.512. Its specific gravity at 25° C. is 1.1465. The acid number is 1.19.

Add to about 25 mg. of isobornyl thiocyanacetate-technical in a small beaker, 5 cc. of two normal alcoholic potassium hydroxide. Cover the beaker with a watch glass and warm on a hot plate for 5 minutes. Acidify one-half of the solution with diluted sulfuric acid and add a few drops of ferric ammonium sulfate T.S.: a red color develops.

Add 1 cc. of 10 per cent ferrous sulfate T.S. to the other half of the solution and warm for another 5 minutes. Make the solution acid to litmus paper with diluted sulfuric acid: a blue color develops in the solution.

Add 1 cc. of two normal alcoholic potassium hydroxide to 5 cc. of a 10 per cent alcoholic solution of isobornyl thiocyanacetate-technical: a yellow color forms which rapidly changes to a deep orange.

Dissolve 10 Gm. of isobornyl thiocyanacetate-technical in 25 cc. of a saturated solution of potassium hydroxide in methanol and reflux on a steam bath for two hours. Pour the solution into 500 cc. of saturated sodium chloride solution, and then acidify with hydrochloric acid. Filter the precipitate on a Buchner funnel, wash with saturated sodium chloride solution and air dry on the filter. Dissolve the precipitate in petroleum ether, add 20 Gm. of anhydrous sodium sulfate, stopper and let stand for several hours. Filter, then evaporate the filtrate to a small volume and cool in an ice bath to effect crystallization. Filter off the crystals, wash with a few cc. of cold petroleum ether, and air dry: the isolated isoborneol melts from 200-205° C.

Determine the nitrogen content of isobornyl thiocyanacetate-technical by the Kjeldahl procedure: the amount of nitrogen found is not less than 4.6 per cent, which is equivalent to an isobornyl thiocyanacetate content of 80 per cent.

**ISOBORNYL THIOCYANOACETATE LOTION:** Pipette 10 cc. of the lotion into a graduated 100 cc. separatory funnel. Add 50 cc. of ether and shake vigorously. Add 10 cc. of alcohol and shake the contents of the flask to break the gel. Allow the funnel to stand and then draw off the lower layer. Dilute the solution remaining in the separatory funnel to 100 cc. with alcohol. Transfer a 10 cc. aliquot to a Kjeldahl flask and determine its nitrogen content; the amount of isobornyl thiocyanacetate-technical is not less than 90 nor more than 110 per cent of the claimed amount.

**LIPIODOL RADIOLOGIQUE ASCENDANT-Fougèra.**—An iodine addition product of poppy-seed oil containing 9.8 to 11.2 per cent of iodine (0.11 Gm. of iodine per cc.) in organic combination.

Lipiodol Radiologique Ascendant is a yellow, oily liquid, which possesses an alliaceous odor and an oleaginous taste, and is insoluble in water. On exposure to air and sunlight it decomposes, turning brown in color. Its specific gravity at 20 C., is from 0.99 to 1.

Lipiodol Radiologique Ascendant conforms to the tests for identity and purity, ash and assay as described in the U. S. Pharmacopeia under Iodized Oil, except that the iodine content found is not less than 9.8 per cent nor more than 11.2 per cent.

**MANNITOL.**— $C_6H_{14}O_6$ .—M. W. 182.17.—1,2,3,4,5,6-Hexahydroxyhexane.

Mannitol occurs as a white, crystalline substance possessing a sweet taste. It melts at 166° to 168° C. It is freely soluble in water and

slightly soluble in alcohol. The refractive index of a 10 per cent aqueous solution at 25° C. is 1.3380.

Add 5 drops of a saturated aqueous solution of mannitol to 1 cc. of ferric chloride T.S. Add 5 drops of distilled water to a second tube containing 1 cc. of ferric chloride T.S. Add 5 drops of 20 per cent sodium hydroxide solution to each tube: a reddish precipitate of ferric hydroxide forms in the tube with no mannitol, and a yellow precipitate forms in the tube containing mannitol. Shake the tubes vigorously: a clear solution appears in the tube containing mannitol, but the precipitate persists in the other tube. Add 5 more drops of the sodium hydroxide solution: no precipitation occurs in the tube containing mannitol, but a further precipitation of ferric hydroxide takes place in the control.

Add 0.5 cc. of acetyl chloride to about 0.1 Gm. of dry mannitol in a test tube. Warm gently (hot water tap) until the solution becomes cloudy. Cool the solution and allow it to stand for a few minutes. Filter off the precipitate and recrystallize it from ether: the recrystallized product melts at 126° C.

To 5 cc. of alkaline cupric citrate solution (Benedict's solution) add 1 cc. of a saturated aqueous solution of mannitol. Heat for five minutes in a boiling water bath: no more than a very slight precipitate occurs.

Dry about 0.50 Gm. of mannitol, accurately weighed, at 110° C. for four hours: the loss in weight does not exceed 0.30 per cent.

Ash about 0.50 Gm. of mannitol, accurately weighed: the residue does not exceed 0.05 per cent.

Dissolve 0.1 Gm. of mannitol, accurately weighed, in distilled water and dilute to 100 cc. in a volumetric flask. Transfer 4 cc. of the solution to a 250 cc. Erlenmeyer flask. Add 50 cc. of potassium periodate reagent prepared by mixing 40 cc. of 5 per cent sulfuric acid (29 cc. sulfuric acid per liter) with 60 cc. of 0.1 per cent potassium periodate (1 Gm. of potassium periodate per liter plus 3 to 5 drops of sulfuric acid). Heat the solution on a steam bath for 15 minutes. Cool to room temperature. Add 5 cc. of chloroform and 1 Gm. of potassium iodide. Allow to stand for five minutes and then titrate the solution with fiftieth-normal sodium thiosulfate. Carry out a blank determination in a similar manner using water in place of the mannitol solution. The difference in titration values of the blank and sample is due to the change in periodate concentration due to oxidation of the mannitol. Each cc. of fiftieth-normal sodium thiosulfate used for the oxidation of mannitol is equivalent to 0.003709 Gm. of mannitol: the mannitol content is not less than 98 per cent or more than 102 per cent.

**MANNITOL SOLUTION:** Determine the density of the mannitol solution by means of a pycnometer. Transfer the mannitol solution from the pycnometer to a volumetric flask of a size calculated to yield a concentration of about 4 mg. of mannitol per 10 cc.

Transfer sufficient solution to contain 4 mg. of mannitol to a 250 cc. Erlenmeyer flask and proceed with the analysis as described in the monograph for mannitol: the mannitol content is not less than 97 per cent or more than 103 per cent of the claimed amount.

**MANNITOL HEXANITRATE.**— $C_6H_8O_{18}N_6$ .—M. W. 452.17.—An explosive compound formed by the nitration of mannitol, a sugar alcohol.

Mannitol hexanitrate tablets are partially soluble in alcohol and in ether (*mannitol hexanitrate*) and are partially soluble in water (*lactose*).

To a powdered tablet of mannitol hexanitrate add one drop of diphenylamine test solution: a characteristic blue color is formed.

The residue obtained in the assay given below melts between 106 and 108 C. (*Caution: The mannitol hexanitrate used in this test may explode on percussion. The operator must be protected by a safety glass screen while determining the melting point.*) It is insoluble in water and soluble in alcohol and in ether. It may be recrystallized from hot alcohol in the form of characteristic long needles in regular clusters.

Transfer an accurately weighed portion of powdered tablets, containing about 0.25 Gm. of mannitol hexanitrate, to a glass stoppered Erlenmeyer flask and extract the powder with 25 cc. of ether; decant the extract through a dry filter paper into a tared dish and repeat the extraction five

times; evaporate the combined filtrates to 3 cc. at a temperature not exceeding 35 C. and allow the remaining solution to evaporate spontaneously. Dry the residue over calcium chloride in a vacuum desiccator for eight hours and weigh the mannitol hexanitrate: the amount of mannitol hexanitrate found corresponds to not less than 93 per cent nor more than 107 per cent of the labeled amount.

**MEPERIDINE HYDROCHLORIDE.**— $C_{15}H_{21}NO_2$ .—M. W. 283.79.—Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride.

Meperidine hydrochloride occurs as a fine, white crystalline, odorless powder; stable in the air at ordinary temperature; soluble in water, acetone and ethyl acetate; slightly soluble in alcohol and isopropylalcohol; and insoluble in benzene and ether. Its aqueous solution (1 in 10) is acid to litmus. Meperidine hydrochloride melts at 186° to 189° C. Aqueous alkali carbonates and hydroxides precipitate the free base as oily droplets which solidify to a colorless or pale yellowish solid.

Dissolve about 0.1 Gm. of meperidine hydrochloride in 5 cc. of water, add 1 cc. of nitric acid followed by 1 cc. of silver nitrate T.S.: a white precipitate of silver chloride, soluble in an excess of strong ammonia solution, results.

To a solution of 0.1 Gm. of meperidine hydrochloride in 5 cc. of ethanol, add 10 cc. of a 3 per cent alcoholic solution of picric acid, with constant stirring; let stand for two hours at room temperature and filter, collecting the meperidine picrate formed, which melts at 190° to 191° C. Dissolve about 0.1 Gm. of meperidine hydrochloride in 1 cc. of water and 1 cc. of U. S. P. alcohol; add 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Saturate about 0.1 Gm. of meperidine hydrochloride dissolved in 10 cc. of water with hydrogen sulfide: no color or precipitate results (*salts of heavy metals*).

Dry about 0.5 Gm. of meperidine hydrochloride, accurately weighed at 100 C., for six hours: the loss in weight does not exceed 1 per cent. Incinerate about 0.5 Gm. of meperidine hydrochloride, accurately weighed: the residue is not more than 0.1 per cent.

Transfer about 0.1 Gm. of meperidine hydrochloride, accurately weighed, to a 500 cc. digestion flask and determine the nitrogen content according to the official method described in *Official and Tentative Methods of Analysis of the Official Association of Agricultural Chemists*, ed. 6, page 26, paragraph 24, using 1.0 Gm. of potassium sulfate, 2.5 cc. of sulfuric acid, a few grains of copper sulfate crystals and digesting about 6 hours: the percentage of nitrogen corresponds to not less than 4.8 per cent nor more than 5 per cent, when calculated to the dried substance.

Transfer about 0.3 Gm. of meperidine hydrochloride, accurately weighed, to a suitable separatory funnel, add 25 cc. of water, followed by the addition of 5 cc. of sodium hydroxide T.S.; extract with five successive portions of ether, using 25 cc., 20 cc., 20 cc., 15 cc. and 10 cc. respectively; wash the combined ether solution with 10 cc. of water, filter through a pledget of cotton and evaporate to a thick oil in a stream of warm air. Reserve the aqueous extract for the chloride determination. Dissolve the oily residue in about 10 cc. of previously neutralized alcohol; warm slightly; add 10 cc. of tenth-normal hydrochloric acid solution, followed by the addition of an equal volume of water; determine the excess acid by titration with fiftieth-normal sodium hydroxide solution, using methyl red T.S. as an indicator: the amount of tenth-normal hydrochloric acid consumed corresponds to not less than 83.5 per cent nor more than 87.5 per cent of ethylmethylphenylpiperidine carboxylate when calculated to the dried substance. Transfer the alkaline aqueous portion from the extraction to a 400 cc. beaker and place on a steam bath to remove the ether, add 100 cc. of water, followed by the addition of 5 cc. of nitric acid and 25 cc. of silver nitrate T.S., subsequently boil, with continuous stirring, and allow to cool in a dark place. Collect the precipitate of silver chloride on a Gooch crucible, wash with 1 per cent nitric acid and water, followed by alcohol and ether; finally dry to constant weight at 105° C.: the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 12.8 per cent nor more than 13.2 per cent, when calculated to the dried substance.

**MERALLURIDE.**— $C_9H_{16}HgN_2O_6 \cdot C_7H_8N_4O_2$ .—M. W. 629.—A mercurial compound derived from equimolecular quantities of mercurated allylsuccinylurea and theophylline.

Meralluride occurs as an odorless white, crystalline powder, possessing a slightly bitter taste. It melts between 197 and 200 C. It is gradually decomposed by light and is incompatible with hydrogen sulfide and fumes of strong acids. An aqueous suspension of meralluride is acid to litmus.

Meralluride is soluble in hot water but is practically insoluble in water, alcohol, chloroform and ether at 25 C.; it is soluble in glacial acetic acid, in aqueous ammonia solution and in sodium hydroxide solution; and it is slowly soluble in sodium bicarbonate solution, with evolution of carbon dioxide.

Place about 0.5 Gm. of meralluride in a small flask, add 5 cc. of water and 3 cc. of formic acid; boil the mixture under a reflux condenser for ten to fifteen minutes: a gray precipitate of metallic mercury is formed. Decant the hot solution through a small filter paper and allow the filtrate to cool (chill in ice water). Collect the crystals of allylsuccinylurea on a small filter paper, wash with two 5 cc. portions of ice water, allow to drain, and dry the crystals over sulfuric acid in a vacuum desiccator for 24 hours: the crystals melt between 145° and 148° C.

Heat the filtrate and washings obtained in the foregoing test to the boiling point and then pass hydrogen sulfide through the solution for ten minutes, filter, cool the filtrate, transfer to a small separatory funnel, add 10 Gm. of sodium acetate and extract with three successive 10 cc. portions of chloroform. Evaporate the combined chloroform extracts nearly to dryness on a water bath and complete the drying by means of a stream of warm air. Suspend the residue in 5 cc. of water, boil to dissolve the residue, filter while hot and cool the filtrate in a bath of ice water to allow crystallization. Filter, wash the crystals with water, allow to drain and dry in a desiccator over sulfuric acid for twenty-four hours: the crystals melt between 270° and 274° C. and respond to identification tests for theophylline.

Suspend about 0.5 Gm. of meralluride in 5 cc. of sodium acetate T.S. and dissolve by the addition of just sufficient sodium hydroxide T.S. (about 8.5 cc.). Filter and divide the filtrate into two portions. To one portion add 0.2 cc. of sodium sulfide solution and compare with the other portion: only a very faint coloration of the test solution is noticeable immediately.

Dry about 1 Gm. of meralluride, accurately weighed, over sulfuric acid in a vacuum desiccator for 24 hours: the loss in weight does not exceed 3.0 per cent.

Ignite about 1 Gm. of meralluride, accurately weighed, in a porcelain crucible: the residue is not more than 0.1 per cent.

Transfer about 0.1 Gm. of meralluride, accurately weighed, to a 50 cc. Erlenmeyer flask fitted with a ground joint, add 15 cc. of nitric acid and a few glass beads; connect the flask to a reflux condenser and heat to boiling for one and one-half hours. Cool; rinse the condenser tube with water, collecting the washings in the flask; transfer the contents of the flask quantitatively to a 400 cc. beaker and dilute to approximately 150 cc. with water. Add 5 cc. of nitric acid and titrate with fiftieth-normal ammonium thiocyanate, using 2 cc. of ferric ammonium sulfate T.S. as an indicator. Use a control solution containing 20 cc. of nitric acid and 2 cc. of the indicator solution in 150 cc. of water to which exactly 0.3 cc. of the fiftieth-normal ammonium thiocyanate has been added. Titrate the unknown solution to the same color intensity as the control and subtract 0.3 cc. from the volume noted in the titration. Each cubic centimeter of fiftieth-normal ammonium thiocyanate is equivalent to 0.002006 Gm. of mercury: the amount of mercury found is not less than 31.0 per cent and not more than 33.0 per cent, calculated to the dried substance.

Transfer about 0.7 Gm. of meralluride, accurately weighed, to a 250 cc. Erlenmeyer flask; add 125 cc. of water and 5 cc. of diluted ammonia solution to dissolve the meralluride. Add exactly 20 cc. of silver nitrate T.S. and warm on a steam bath until the white precipitate coagulates; cool to 30-40° C. and filter through a medium porosity fritted glass

crucible, transferring the precipitate and washing with five 10 cc. portions of warm (40° C.) water until the wash water tests free of silver ion with sodium chloride solution acidified with nitric acid. Dissolve the precipitate on the fritted glass filter with 4 to 5 cc. of nitric acid; allow the nitric acid solution to filter into a clean flask without suction, and finally wash the crucible with hot water until the filtrate and washings approximate 150 cc.; cool; add 1 cc. of ferric ammonium sulfate T.S.; and titrate with tenth-normal ammonium thiocyanate solution. Use a control containing the same volumes of water and nitric acid, with 1 cc. of the indicator solution to determine any blank correction. Each cubic centimeter of tenth-normal ammonium thiocyanate is equivalent to 0.01802 Gm. of anhydrous theophylline. The amount of anhydrous theophylline found is not less than 29.0 per cent and not more than 31.0 per cent, calculated to the dried substance.

**MERALLURIDE SODIUM SOLUTION.**—A sterile aqueous solution containing in each cubic centimeter approximately 119 mg. of meralluride ( $C_9H_{16}HgN_2O_6$ .—M. W. 448.84) and 13 mg. of theophylline ( $C_7H_8N_4O_2$ .—M. W. 180.17), adjusted with sodium hydroxide to a pH of about 7.5. Each 1 cc. of meralluride sodium solution contains the equivalent of 39 mg. of mercury and 48 mg. of theophylline-U. S. P.

Meralluride sodium solution is clear, colorless to pale yellow and odorless and possesses a bitter taste. The pH of the solution is between 7.4 and 7.6 at 25 C. Meralluride sodium solution should be protected from light.

Five cubic centimeters of meralluride sodium solution responds to tests for the presence of mercury, allylsuccinylurea and theophylline given under Meralluride-N. N. R. Evaporate 1 cc. of meralluride sodium solution to dryness in a tared porcelain dish and ignite; the residue responds to tests for sodium.

To 5 cc. of meralluride sodium solution add 0.5 cc. of sodium acetate T.S. and 0.3 cc. of diluted acetic acid; dilute to 10 cc. with water and divide the solution into two portions. Add to one portion 0.2 cc. of sodium sulfide T.S. and compare with the other portion; only a very faint difference in color of the solution tested is noticeable immediately.

Determine the mercury content of 2 cc. of meralluride sodium solution, accurately measured, by the method given under Meralluride-N. N. R.: the amount of mercury found is not less than 95 per cent nor more than 105 per cent of 39 mg. per cubic centimeter.

Determine the theophylline content of 5 cc. of meralluride sodium solution, accurately measured, by the method given under Meralluride-N. N. R.: the amount of anhydrous theophylline found is not less than 95 per cent and not more than 105 per cent of 43.6 mg. per cubic centimeter.

**MERCOCRESOLS.**—A mixture consisting of equal parts by weight of *secondary*-amyltricresol and *ortho*hydroxyphenylmercuric chloride.

*Secondary*-amyltricresol ( $C_{12}H_{18}O$ .—F. W. 178.26) is a mixture of isomeric *secondary*-amyl cresols obtained by the reaction of cresol and *sec*-amyl alcohol. It appears as a yellowish liquid, which darkens on exposure to light and air, and possesses a phenol-like odor. It is miscible with the common organic solvents (acetone, alcohol, benzene, chloroform, ether); soluble in solutions of fixed alkalis forming a cloudy solution; slightly soluble in water; soluble in an aqueous solution of 10 per cent acetone and 50 per cent alcohol from which it does not precipitate on addition of water. A saturated aqueous solution is neutral or slightly acid to litmus. It gives no color reaction with ferric chloride T.S. (*cresol*). At a pressure of 5 mm. of mercury not less than 95 per cent distills between 115° and 130° C. The refractive index is 1.5140-1.5190 at 25° C. The specific gravity is 0.95-0.98 at 25° C.

*o*-Hydroxyphenylmercuric chloride ( $C_6H_5OHgCl$ .—M. W. 329.26) is

a white or slightly buff colored, crystalline powder; soluble in alcohol, ether, acetone, mineral acids and in solutions of fixed alkalis; very slightly soluble in water; and soluble in an aqueous solution of 10 per cent acetone and 50 per cent alcohol. It melts at 147-151° C. The saturated aqueous solution is slightly acid to litmus. A 0.1 per cent solution in diluted nitric acid yields the following qualitative reactions: the addition of ammonium sulfide T.S. gives no precipitate within five minutes but on warming over a steam bath a black precipitate is formed; on warming with silver nitrate T.S. it yields a white precipitate soluble in excess strong ammonia solution; when treated with an excess of sodium hydroxide T.S. it yields no yellow precipitate (*mercuric ion*) and the color does not darken (*mercurous ion*).

*o*-Hydroxyphenylmercuric chloride gives no color reaction with ferric chloride T.S. It yields not more than 0.1 per cent of residue on ignition. There is no apparent loss of weight on drying in a vacuum over phosphorus pentoxide for 24 hours. The alcohol-insoluble residue does not exceed 2 per cent of the original sample.

Transfer 300 mg. of *o*-hydroxyphenylmercuric chloride, accurately weighed, to a 250 cc. beaker containing 5 cc. of hydrochloric acid and 150 cc. of water, and heat on a steam bath until solution is complete. Saturate the warm solution with hydrogen sulfide and allow to stand until the precipitated mercuric sulfide has settled. Filter on a Gooch crucible and wash with water, alcohol, ether, carbon disulfide and ether in the order listed. Dry in an oven at 100-110° C. for one-half hour and finally cool in a desiccator: the weight of mercuric sulfide found multiplied by 0.8622 is equivalent to a mercury content of not less than 60.5 per cent nor more than 61.6 per cent.

### MERCURIC POTASSIUM IODIDE.— $K_2HgI_4$ .—M. W. 787.

Mercuric potassium iodide occurs as yellow crystals, deliquescent in air. It is soluble in alcohol and in potassium iodide T.S. It yields a clear solution with one part of water. When the solution is diluted with much water, mercuric iodide precipitates slowly; but if one fifth of its weight of potassium iodide is previously added to the salt or its concentrated solution, no mercuric iodide separates on dilution. Its aqueous solution is slightly alkaline to litmus. When the salt is heated in a test tube to the point of fusion, it becomes red, but on cooling again assumes a yellow color; at higher temperatures, there is volatilization of mercuric iodide.

Treat about 0.2 Gm. of mercuric potassium iodide with 1 cc. of water and add 1 cc. of chloroform and 0.5 cc. of ferric chloride T.S.: the chloroform shows the characteristic color of iodine. Treat about 0.1 Gm. of the salt with 2 cc. of sodium hydroxide T.S. and add a few drops of formaldehyde T.S.: a black precipitate of metallic mercury is produced.

Mercuric potassium iodide loses not more than 4 per cent of its weight when dried at 120 C. for four hours.

Transfer about 1.5 Gm. of mercuric potassium iodide, accurately weighed, to a 100 cc. volumetric flask, and dissolve in 1.5 cc. of water, then dilute to 100 cc. Immediately pipette 10 cc. of the solution into a glass stoppered 250 cc. bottle and add 35 cc. of hydrochloric acid and 5 cc. of chloroform. Titrate the solution with tenth-normal potassium iodate (10.701 Gm. in 1,000 cc.), stoppering the bottle and shaking the contents well after each addition. The addition of the potassium iodate solution is continued until the iodine which was first liberated disappears, and the chloroform shows no pink color: the iodine content, calculated to the dry salt, is not less than 63.4 per cent nor more than 65.5 per cent.

Dissolve about 2.5 Gm. of mercuric potassium iodide, accurately weighed, in about 10 cc. of water, and add sufficient potassium iodide solution to prevent precipitation of mercuric iodide. Introduce the solution and washings into a tared cathode cup and add 10 cc. of 20 per cent sodium hydroxide solution. Pass through the solution a direct electric current, gradually increasing the strength of the current so that at the end of eight minutes it will be 2 to 3 amperes and 7 to 10 volts, stirring the solution by rotating the anode about 500 revolutions per minute. After 40 minutes, wash with distilled water, with the aid of a siphon and



without interrupting the current, until the current drops to zero. Remove the cathode cup and allow it to stand in 20 cc. of 3 per cent acetic acid solution until bubbles cease to be evolved. Wash the mercury with water, and then alcohol, remove most of the excess alcohol by filter paper, then dry in a desiccator over potassium hydroxide sticks and a beaker of mercury. The increase in the weight in the cathode cup represents the amount of mercury present in the quantity of the salt taken. The mercury content of mercuric potassium iodide, calculated to the dry salt, is not less than 25.0 per cent, nor more than 26.0 per cent.

**MERTHIOLATE-Lilly.**— $C_9H_9HgNaO_2S$ .—M. W. 404.83.  
—Sodium ethylmercuri-thiosalicylate.

Merthiolate occurs as a light cream colored, nonhygroscopic, crystalline powder, having a slight odor. It is stable in air but unstable in sunlight. One part by weight of Merthiolate dissolves in approximately 1 part of water or in approximately 8 parts of alcohol. It is practically insoluble in ether and benzene. A 1 per cent solution in water has a  $pH$  value of about 6.7.

Add diluted sulfuric acid to a solution of Merthiolate: a white precipitate of ethylmercurithiosalicylic acid is produced. Recrystallize this product from 95 per cent alcohol and dry in a vacuum over sulfuric acid; it melts at 111-114 C. Bubble carbon dioxide into a 1 per cent solution of Merthiolate: a precipitate is produced which is soluble in sodium hydroxide. Add a few drops of silver nitrate T.S. to a 1 per cent solution of Merthiolate: a white precipitate separates. Add a few drops of lead acetate T.S. to a 1 per cent solution of Merthiolate: a white precipitate separates. Add a few drops of cupric sulfate T.S. to a 1 per cent solution of Merthiolate: a green precipitate separates.

Shake 0.5 Gm. of Merthiolate, accurately weighed, with 20 cc. of anhydrous ether for ten minutes; filter, evaporate the ether and dry in a vacuum over sulfuric acid to constant weight: the weight of the residue does not exceed 3 mg. Dissolve about 0.2 Gm. of Merthiolate in 5 cc. of sulfuric acid: not more than a slight yellow color is produced. Mix equal parts of a 1 per cent solution of Merthiolate and of ammonium sulfide T.S.: a white precipitate is formed, which does not blacken on standing 48 hours. Dry 0.1 Gm. of Merthiolate to constant weight in a vacuum over sulfuric acid: it does not lose more than 0.5 per cent in weight.

Transfer about 0.2 Gm. of Merthiolate, accurately weighed, to a 100 cc. beaker, dissolve in 75 cc. of water, adding 5 cc. hydrochloric acid and 3 cc. of bromine; heat on a water bath until fumes of bromine no longer appear and the solution is colorless; cool and completely saturate with hydrogen sulfide; collect the precipitate on a tared Gooch crucible; wash with alcohol, ether, carbon disulfide and finally with ether; dry to constant weight at 100 C.: the percentage of mercury corresponds to not less than 49.1 per cent nor more than 49.6 per cent when calculated to the dried substance.

**MESTILBOL.**— $C_{19}H_{22}O_2$ .—M. W. 282.37.—3-*p*-Hydroxyphenyl-4-*p*-methoxyphenyl-3-hexene.

Mestilbol occurs as an odorless, white, crystalline powder, which melts at 116-117.5 C. when recrystallized from benzene-petroleum ether (112-114° C., when recrystallized from alcohol). It is soluble in alcohol; freely soluble in acetone and in ether; and practically insoluble in water, in dilute mineral acids and in dilute aqueous solutions of sodium and potassium hydroxide. It may be dissolved in vegetable oils and in dilute solutions of sodium or potassium hydroxide in 50 per cent alcohol.

To 1 mg. of mestilbol dissolved in 5 cc. of alcoholic potassium hydroxide T.S. add diluted hydrochloric acid to neutralize the solution and then add 1 cc. in excess. Add 1 cc. of molybdophosphotungstate T.S. and shake. Allow to stand ten minutes, dilute to 25 cc. with water and add 5 cc. of saturated sodium carbonate solution: a blue color develops on standing. Add a few drops of 50 per cent solution of antimony pentachloride in dry alcohol-free chloroform to a dilute solution of mestilbol in the same solvent: a red colored solution is produced which changes rapidly to purple (*distinction from hexestrol, which gives no color*).

Dissolve 10 mg. of mestilbol in 5 cc. of concentrated sulfuric acid: an orange color is produced which disappears on dilution with water (*distinction from hexestrol and benzaestrol, which give no color*).

Dry an accurately weighed specimen of mestilbol at 100° C. for four hours: the loss does not exceed 0.5 per cent. Ignite an accurately weighed specimen of mestilbol after the addition of concentrated sulfuric acid: the sulfated ash residue is not more than 1 per cent.

Transfer 0.1 Gm. of mestilbol to a 100 cc. volumetric flask and dilute to the mark with carbon tetrachloride. Transfer 10 cc. of the solution to a 250 cc. iodine flask fitted with an accurately ground stopper; add the calculated quantity plus 1 cc. of tenth-normal bromide-bromate solution (prepared according to the *U. S. P. XIII*, p. 853); wash the walls of the flask and wet the stopper by the addition of 10 cc. of distilled water. Quickly add 10 cc. of 10 per cent hydrochloric acid and insert the wet stopper. Shake the mixture thoroughly for several minutes, then place the flask in the dark at 25-30° C. for exactly 50 minutes. Shake the flask intermittently during this period. At the end of 50 minutes place 2 cc. of 40 per cent potassium iodide solution around the stopper. Remove the stopper just enough to allow the potassium iodide solution to enter the flask, shake thoroughly, rinse the stopper and sides of the flask with distilled water, add 25 cc. of carbon tetrachloride and titrate with fiftieth-normal sodium thiosulfate to the disappearance of the pink color in the carbon tetrachloride. Each cubic centimeter of tenth-normal bromide-bromate solution is equivalent to 4.706 mg. of mestilbol. The mestilbol content is not less than 99 per cent. *The nature of the reaction between bromine and mestilbol leads to complications unless the conditions of the procedure given are strictly observed. This method of standardization must be considered tentative until more accurate analytic procedures are available.*

**METHACHOLINE BROMIDE.** —  $C_8H_{18}BrNO_2$ . — M. W. 240.15 — Acetyl- $\beta$ -methylcholine bromide. — Trimethyl- $\beta$ -acetoxy-propyl ammonium bromide.

Methacholine bromide occurs as a white, crystalline, very hygroscopic powder, possessing a slight fishy odor. It is readily soluble in water and alcohol, insoluble in benzene and ether. The aqueous solution is neutral to litmus. Methacholine bromide melts at 147-149° C.

Dissolve about 1 Gm. of Methacholine bromide in 10 cc. of water; to a 1 cc. portion add 1 cc. of alcohol and 1 cc. of sulfuric acid and heat in a steam bath: the odor of ethyl acetate becomes perceptible. To another 5 cc. portion add 2.5 Gm. of potassium hydroxide and heat: odor of trimethylamine is noticed. To the remaining portion add an excess of silver nitrate T.S.: a white, curdy precipitate soluble in strong ammonia solution results. Add 3 cc. of a 20 per cent aqueous solution of sodium perchlorate to 2 cc. of a 10 per cent solution of methacholine bromide; shake thoroughly and cool in ice water: no precipitate is formed (*acetylcholine*). Moisten about 0.1 Gm. of methacholine bromide with a 5 per cent solution of platinic chloride: small rhombohedral plates are formed (*distinction from acetylcholine chloride, which forms needles, and choline chloride, which forms no crystals*). Dissolve 0.2 Gm. of methacholine bromide in 2 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substance*).

Dry about 0.5 Gm. of methacholine bromide, accurately weighed, to constant weight at 110° C.: the loss in weight does not exceed 1.5 per cent. Incinerate about 0.5 Gm. of methacholine bromide, accurately weighed, in a platinum crucible: the residue does not exceed 0.1 per cent.

Transfer about 0.5 Gm. of methacholine bromide, previously dried at 105° C. to 110° C., to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the official method described in *Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, p. 26, paragraph 24: the percentage of nitrogen is not less than 5.6 nor more than 5.9.

Dissolve about 0.4 Gm. of methacholine bromide, previously dried at 105° C. to 110° C. and accurately weighed, in 15 cc. of water in an Erlenmeyer flask; add 40 cc. of tenth normal sodium hydroxide solution and heat on the steam bath for 45 minutes; stopper and allow to cool; titrate the excess of sodium hydroxide with tenth normal hydrochloric acid,

using phenolphthalein T.S. as an indicator: the amount of acetyl ( $\text{CH}_3\text{CO}-$ ) is not less than 17.5 per cent nor more than 18.3 per cent.

Transfer about 0.4 Gm. of methacholine bromide, previously dried at  $105^\circ\text{C}$ . to  $110^\circ\text{C}$ . and accurately weighed, to a 100 cc. volumetric flask, dissolve in 50 cc. of water, with agitation add 30 cc. of silver nitrate T.S., add 5 cc. of nitric acid, and finally add water to final volume and mix thoroughly. Filter through a dry filter into a dry flask, rejecting the first filterful; titrate 50 cc. of the filtrate with tenth normal ammonium thiocyanate solution using ferric ammonium sulfate T.S. as an indicator: the amount of bromine is not less than 32.9 per cent nor more than 33.5 per cent.

**METHADONE HYDROCHLORIDE.**— $\text{C}_{21}\text{H}_{27}\text{NO}\cdot\text{HCl}$ .  
— M. W. 345.90. — 6-Dimethylamino-4,4-diphenyl heptanone-3-hydrochloride.

Methadone hydrochloride occurs as colorless crystals or as a white crystalline powder, which is odorless and possesses a bitter taste. It is soluble in water, freely soluble in alcohol and in chloroform, practically insoluble in ether, and insoluble in glycerin. It is much more soluble in diluted sulfuric acid than in diluted nitric acid, and is slightly soluble in diluted hydrochloric acid. It is incompatible with alkaline solutions and with syrup of wild cherry, U. S. P. It is precipitated from solution by the common alkaloidal reagents. The pH of a 1 per cent aqueous solution of methadone hydrochloride is between 4.5 and 6.5. It melts at  $232\text{--}235^\circ\text{C}$ . An aqueous solution of methadone hydrochloride, 30 mg. per 100 cc., exhibits an ultraviolet absorption maximum at  $2920\text{ \AA}$ .,

$$\left(\frac{E}{1\text{ cm.}}\right)_{1\%} = 15.6 \pm 0.1.$$

Dissolve about 0.1 Gm. of methadone hydrochloride in 10 cc. of water and add a clear, filtered solution of 0.125 Gm. of picrolonic acid dissolved in 50 cc. of boiling distilled water. Stir the mixture until the yellow precipitate is well formed and allow the mixture to stand for two hours. Filter and recrystallize the residue from diluted alcohol. Filter and dry the residue: the product melts at  $160\text{--}162^\circ\text{C}$ .

Dissolve about 10 mg. of methadone hydrochloride in 2 cc. of water. Add 2 cc. of methyl orange T.S.: a yellow precipitate forms.

Dissolve about 10 mg. of methadone hydrochloride in 10 cc. of water, add 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S.: a white precipitate forms which is soluble in excess ammonia T.S.

Dry about 1 Gm. of methadone hydrochloride, accurately weighed, for 24 hours at  $100^\circ\text{C}$ .: the loss in weight does not exceed 0.3 per cent.

Ignite about 0.1 Gm. of methadone hydrochloride, accurately weighed: the residue does not exceed 0.1 per cent.

Transfer about 0.5 Gm. of methadone hydrochloride, accurately weighed, to a 250 cc. flask and dissolve it in 50 cc. of water. Titrate with tenth-normal silver nitrate, using 10 drops of dichlorofluorescein T.S. as the indicator. Each cc. of tenth-normal silver nitrate corresponds to 3.546 mg. of chloride: the amount of chlorine found is not less than 10.0 per cent nor more than 10.5 per cent, calculated to the dried substance. Transfer about 0.1 Gm. of methadone hydrochloride, accurately weighed, to a suitable Kjeldahl flask and determine the nitrogen content by the semimicro method, U. S. P. *XIII*, p. 672: the amount of nitrogen found is not less than 3.95 per cent nor more than 4.15 per cent, calculated to the dried substance.

Dissolve about 0.15 Gm. of methadone hydrochloride, accurately weighed, in 50 cc. of water in a separatory funnel. Add 20 cc. of ammonia T.S., and extract the methadone base with four successive portions of 40 cc., 20 cc., 20 cc., and 15 cc. of ether. Combine the ether extracts in a beaker and carefully evaporate the ether on a water bath in a stream of warm air. Dissolve the residue in 15 cc. of neutralized alcohol and titrate the solution with fiftieth-normal hydrochloric acid using methyl red T.S. as the indicator. Near the end of the titration add 50 cc. of water. Each cc. of fiftieth-normal hydrochloric acid is equivalent

to 6.19 mg. of methadone base. The amount of methadone base found corresponds to not less than 88.5 per cent nor more than 90.0 per cent, calculated to the dried substance.

**METHENAMINE TETRAIODIDE.**— $C_6H_{12}I_4N_4$ .—M. W. 647.89.—Hexamethylenetetramine tetraiodide.

Methenamine tetraiodide is a red powder, having a slight, but characteristic, odor and taste. When heated (*caution!*) to  $138^\circ C.$ , it decomposes with violence.

Methenamine tetraiodide is slightly soluble in acetone, alcohol, chloroform, carbon disulfide and ether (with partial decomposition). It is almost insoluble in water, but dissolves with decomposition in aqueous solutions of alkali iodides and of sodium thiosulfate and in diluted hydrochloric acid.

Heat 5 Gm. of methenamine tetraiodide with 15 cc. of diluted sulfuric acid: first vapors of iodine (recognized by their color and effect on starch paper) are evolved; later, formaldehyde is given off (recognized by its odor and the blackening of paper moistened with silver-ammonium nitrate T.S.) Heat the methenamine tetraiodide-sulfuric acid mixture until it is colorless; add an excess of sodium hydroxide T.S.: ammonia is evolved (recognized by its odor and effect on red litmus paper). To 0.5 Gm. of methenamine tetraiodide add a drop of sulfuric acid: decomposition occurs with evolution of brown fumes.

Warm 0.5 Gm. of methenamine tetraiodide with 0.5 cc. of water until a clear solution results: the addition of a few drops of barium chloride T.S. does not produce a precipitate (*sulfates*).

Ignite a weighed quantity of methenamine tetraiodide: not more than 0.03 per cent of ash remains.

The iodine content of methenamine tetraiodide is 78.5 per cent.

**METHIODAL SODIUM.**— $CH_2INaO_3S$ .—M. W. 244.0.—The sodium salt of mono-iodomethanesulfonic acid.

Methiodal sodium occurs as a white, crystalline, odorless powder possessing a slight saline taste followed by a sweetish after-taste; it is very soluble in methyl alcohol, slightly soluble in ethyl alcohol, practically insoluble in acetone, benzene and ether; the aqueous solution is neutral to litmus; on exposure to light it decomposes, turning to a yellow color.

Fuse about 0.5 Gm. of methiodal sodium with 5 Gm. of powdered anhydrous sodium carbonate in a nickel crucible until decomposed. Allow the crucible and contents to cool; dissolve the residue in 20 cc. of water; filter the mixture through paper and divide the filtrate into two portions. To one portion add an excess of diluted hydrochloric acid followed by the addition of a few drops of freshly prepared 10 per cent sodium nitrite solution and finally a few drops of chloroform and agitate the mixture: a deep violet color is assumed by the chloroform. To the other portion add a few drops of freshly prepared sodium nitroprusside T.S.: a deep violet color results. To about 0.1 Gm. of methiodal sodium dissolved in 5 cc. of water, add an excess of acetic acid, followed by the addition of an equal volume of cobalt uranyl acetate T.S.: a yellow crystalline precipitate results. Dissolve about 1 Gm. of methiodal sodium in 25 cc. of water; separate portions of 5 cc. each yield no opalescence or at most a slight opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*inorganic iodide and chloride*); no turbidity with 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride T.S. (*sulfate*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*). When tested for arsenic according to the U. S. P. the product meets requirements for arsenic.

Dry about 0.2 Gm. of methiodal sodium, accurately weighed, to constant weight at  $100^\circ C.$ : the loss in weight does not exceed 1 per cent.

Do a Carius determination on about 0.3 Gm. of methiodal sodium: the iodine found corresponds to not less than 51.9 per cent nor more than 52.3 per cent when calculated to the dried substance. Weigh accurately about 0.3 Gm. of methiodal sodium in a tared platinum dish, add 5 cc. of sulfuric acid, gently heat while the fumes of iodine and sulfur trioxide

are evolved. Repeat twice, using two portions of 2 cc. of sulfuric acid each time. Cool and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 9.3 per cent, nor more than 9.5 per cent calculated to the dried substance.

**METRAZOL.**— $C_6H_{10}N_4$ .—M. W. 138.17.—Pentamethylene-tetrazol.

Metrazol occurs as biaxial, optically negative, white crystals that are freely soluble in water. It melts at 57-58° C.

To a 10 per cent aqueous solution of metrazol add 10 cc. of saturated solution of mercuric bichloride: a white precipitate results, which may be recrystallized from hot water or alcohol to yield crystals melting at 177-178° C. and leaving not more than 0.1 per cent of ash on incineration.

Transfer about 0.2 Gm. of metrazol, accurately weighed, to a wide mouth weighing bottle; allow to stand over calcium chloride: the loss in weight is not more than 0.1 per cent.

Transfer about 0.2 Gm. of metrazol, accurately weighed, to a platinum dish and ignite: the ash is not weighable.

Determine the nitrogen content by the Dumas method: the nitrogen is not less than 40.4 nor more than 40.9 per cent.

**METYCAINE HYDROCHLORIDE-Lilly.**— $C_{16}H_{23}NO_2$  HCl.—M. W. 297.82. — *d,l*-3-Benzoxo-1-(2-methylpiperidino) propane hydrochloride.

Metycaine Hydrochloride occurs as a fine, white, crystalline, odorless powder. When applied to the tongue, it produces a slightly bitter taste that is followed by a sense of numbness. It is stable in air. Metycaine Hydrochloride is freely soluble in water, about 1 in 1; soluble in alcohol and chloroform; and insoluble in ether and olive oil. Its aqueous solution (1 in 10) is faintly acid to litmus. It is optically inactive. Metycaine Hydrochloride melts at from 172° to 175° C. Alkali carbonates and hydroxides precipitate the free base from aqueous solutions as a water-white to a light yellowish oil which does not solidify at ordinary temperatures.

Dissolve about 1 Gm. of Metycaine Hydrochloride in 10 cc. of water; divide into 2 cc. portions. To one portion add 1 cc. of diluted sulfuric acid and 1 cc. of potassium permanganate T.S.: the color is discharged. To a second portion add 1 cc. of gold chloride solution: a yellow precipitate appears; to a third portion add 2 drops of diluted hydrochloric acid, 2 drops of a 10 per cent sodium nitrite solution and gradually mix with a solution of 0.2 Gm. of beta-naphthol in 10 cc. of a 10 per cent sodium hydroxide solution: a white precipitate appears and changes to a yellowish, and finally to a greenish yellow color, increasing in intensity as the concentration of the beta-naphthol increases (*distinction from the anesthetics responding to the diazo-reaction*). Dissolve about 0.1 Gm. of Metycaine Hydrochloride in 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*). Dissolve about 0.5 Gm. in 50 cc. of water: separate portions of 5 cc. each yield no turbidity with 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride T.S. (*sulfate*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Dry about 0.5 Gm. of Metycaine Hydrochloride, accurately weighed, over sulfuric acid in a desiccator for 48 hours: the loss in weight does not exceed 0.25 per cent. Ignite about 0.5 Gm., accurately weighed: the residue is not more than 0.2 per cent. Transfer about 0.25 Gm. to a 400 cc. beaker, add 100 cc. of water, followed by the addition of 25 cc. of tenth-normal silver nitrate solution and 3 cc. of nitric acid, boil with continuous stirring and allow to cool in a dark place. Collect the precipitate of silver chloride on a Gooch crucible, wash with 1 per cent nitric acid, followed by alcohol and ether; finally dry to constant weight at 105° C.: the amount of hydrogen chloride calculated from the silver chloride found corresponds to not less than 12 per cent, nor more than 12.35 per cent calculated to the dried substance.

Transfer about 0.25 Gm. of Metycaine Hydrochloride, accurately

weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by the addition of 5 cc. of diluted ammonia solution, extract with seven successive portions of chloroform, using 35 cc., 30 cc., 25 cc., 20 cc., 15 cc., 10 cc., and 10 cc., respectively; wash the combined chloroform extracts, with 15 cc. of water, filter through a pledget of cotton and evaporate to a thick oil in a stream of warm air; dissolve the oily residue in about 10 cc. of previously neutralized alcohol; warm slightly; add 10 cc. of tenth-normal hydrochloric acid, followed by the addition of an equal amount of water; determine the excess of acid by titration with twentieth-normal sodium hydroxide, using methyl-red T.S. as an indicator: the amount of tenth-normal hydrochloride acid consumed corresponds to not less than 86.5 per cent, nor more than 88 per cent 3-benzoxo-1-(2-methyl-piperidino)propane.

**NAPHAZOLINE HYDROCHLORIDE.**— $C_{14}H_{13}N_2$ . HCl.—M. W. 246.73.—2(1-Naphthyl-methyl)imidazoline hydrochloride.

Naphazoline hydrochloride occurs as a white, odorless, crystalline powder possessing a bitter taste. It is freely soluble in water and in alcohol, very slightly soluble in chloroform and practically insoluble in benzene and in ether.

Naphazoline hydrochloride melts between  $255^{\circ}$  and  $260^{\circ}$  C. A 1 per cent solution of naphazoline hydrochloride is clear and colorless; it has a  $pH$  of about 6.2 and responds to tests for chlorides.

Place about 0.5 Gm. of naphazoline hydrochloride in a separatory funnel, add 25 cc. of water saturated with sodium chloride and 5 cc. of 10 per cent sodium hydroxide solution. Extract the mixture with five 15 cc. portions of residue-free ether; wash the combined ether extracts with two 5 cc. portions of water; filter, and evaporate the ether solution to near dryness on a water bath. Remove the remainder of the ether in a stream of warm air and dry the residue at  $70^{\circ}$  C.: the melting point of a portion of the characteristic crystalline residue is between  $117^{\circ}$  and  $120^{\circ}$  C.

A 0.05 per cent solution of naphazoline hydrochloride yields a white precipitate with phosphotungstic acid T.S., a mauve crystalline precipitate melting at  $158$  to  $160$  C. with Reinecke's salt and a yellowish crystalline precipitate (*Caution!*) melting at  $193^{\circ}$  to  $196^{\circ}$  C. with picric acid.

Dry about 0.5 Gm. of naphazoline hydrochloride, accurately weighed, for four hours at  $70$  C.: the loss in weight does not exceed 0.4 per cent. Ignite about 0.5 Gm. of naphazoline hydrochloride, accurately weighed: the residue is not more than 0.2 per cent.

Transfer about 0.2 Gm. of naphazoline hydrochloride, accurately weighed, to a suitable Kjeldahl flask and determine the nitrogen content according to the method described in *Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, p. 26, paragraph 26: the amount of nitrogen is not less than 11.15 per cent nor more than 11.40 per cent when calculated to the dried substance.

Transfer about 0.2 Gm. of naphazoline hydrochloride, accurately weighed, to a 400 cc. beaker and determine the chlorine content according to the method as described in *Methods of Analysis of the A. O. A. C.*, ed. 6, p. 34, paragraph 48: the amount of chlorine found corresponds to not less than 14.15 per cent nor more than 14.40 per cent when calculated to the dried substance.

Transfer about 0.2 Gm. of naphazoline hydrochloride, accurately weighed, to a separatory funnel; add 5 cc. of water to dissolve the salt and then add 10 cc. of sodium hydroxide T.S. previously saturated with sodium chloride. Extract the mixture with six portions (25, 20, 15, 10, 10 and 10 cc.) of ether; wash the combined ether extracts with two 5 cc. portions of water; extract the water washings with two 10 cc. portions of ether and combine these extracts with the main ether extract. Evaporate the ether solution, contained in a beaker, to near dryness on a water bath and complete the removal of ether in a stream of cool air; add 10 cc. of neutral alcohol to dissolve the residue, dilute to about 50 cc. with water and titrate with twentieth-normal hydrochloric acid, using methyl red T.S. as the indicator. Each cubic centimeter of twentieth-normal

hydrochloric acid is equivalent to 0.01234 Gm. of naphazoline hydrochloride: the naphazoline hydrochloride content found is not less than 97.0 per cent.

**NIKETHAMIDE.**— $C_{10}H_{14}N_2O$ .—M. W. 178.23.—The diethylamide of nicotinic acid.

Nikethamide occurs as a clear, colorless to very pale yellowish, somewhat viscous liquid, possessing a slight characteristic aromatic odor and a peculiar bitter taste. Nikethamide is miscible in all proportions with water, alcohol and ether. The refractive index of nikethamide is 1.522 to 1.524 at 25 C.; the specific gravity is not less than 1.058 nor more than 1.066 at 25 C. The  $pH$  of a 25 per cent aqueous solution (W/V) of nikethamide made with freshly boiled and cooled distilled water is not below 6.0 or above 6.5, as determined by means of a glass electrode. Nikethamide freezes on standing in the cold and melts at from 20 to 26 C.; it resolidifies easily when cooled, provided some fragmentary crystals are present. Nikethamide boils at 128° to 129° C. at 3 mm. of mercury, at 158° to 159° C. at 10 mm. of mercury and at about 296° to 300° C., with some decomposition at one atmosphere.

Dissolve about 3.0 Gm. of nikethamide in 10 cc. of 10 per cent sodium hydroxide solution and warm on a water bath for thirty minutes: the solution yields the odor of diethylamine. Allow the solution to cool; acidify with diluted hydrochloric acid to a  $pH$  of 3.6 (slightly acid to congo red); collect the fine, white precipitate on a filter, wash with water and recrystallize from 5 cc. of water; collect on a filter and dry at 100° C.: the nicotinic acid obtained melts at 235-238 C.

Heat a few drops of nikethamide with 1 Gm. of sodium carbonate: a strong odor of pyridine results.

Dissolve 10 Gm. of nikethamide in 90 cc. of water: the solution is clear, nearly colorless and free from the odor of pyridine: it yields only a faint odor of diethylamine. The solution will respond to the following tests: Add to 5 cc. of solution 5 cc. of normal hydrochloric acid and 5 cc. of a solution made by dissolving 12 Gm. of potassium iodide, 3 Gm. of bismuth subnitrate and 3 cc. of concentrated nitric acid in sufficient water to make a volume of 50 cc.: a heavy reddish orange precipitate forms immediately. Add to 5 cc. of the solution 5 cc. of cupric sulfate T.S. and 5 cc. of potassium thiocyanate T.S.; shake the mixture: a flocculent light green precipitate forms. A 10 cc. portion of the solution is yellow on the addition of 5 drops of methyl red indicator (*free acid*) but turns red on the addition of 0.1 cc. of tenth-normal hydrochloric acid (*limit of free diethylamine*). A 5 cc. portion of the solution becomes only faintly opalescent on the addition of 0.5 cc. of nitric acid and 0.5 cc. of silver nitrate T.S. (*chloride*). Mix 5 cc. of the solution with 5 cc. of sulfuric acid, cool and cautiously overlay 5 cc. of 5 per cent of ferrous ammonium sulfate solution: no brown color appears at the interface (*nitrate*). Add 5 drops of diluted sulfuric acid to 5 cc. of the solution; extract twice in a separatory funnel with 20 cc. portions of a mixture of 3 parts of chloroform and 1 part of isopropyl alcohol; combine the extracts, filter, evaporate to dryness on a steam bath and dissolve the dry residue in 10 cc. of boiling water. When the solution is cool, add 0.1 cc. of tenth-normal sodium hydroxide and 1 drop of phenolphthalein T.S.: the solution turns red (*nicotinic acid*).

Warm 1.0 Gm. of nikethamide for one hour with 3 cc. of diluted hydrochloric acid and 6 cc. of water; cool and add 5 cc. of sodium hydroxide T.S.: the solution yields no distinct yellow color (*foreign organic impurities*).

A solution made by dissolving 1 Gm. of nikethamide in 5 cc. of carbon disulfide is clear (*water*).

Ash 1 Gm. of nikethamide: the residue is not more than 0.5 mg.

Transfer 25 mg. to 50 mg. of nikethamide, accurately weighed, to a 50 cc. Kjeldahl digestion flask and add 1 cc. of water and 1 cc. of concentrated sulfuric acid. Heat the mixture gently until most of the water has been removed and continue heating vigorously for fifteen minutes; cool, add 3 cc. of water, transfer to a micro Kjeldahl distilling apparatus, add 5 cc. of sodium hydroxide solution (1:1) and distil into a flask containing 10 cc. of 2 per cent boric acid solution colored with methyl red solution (1 drop in each 20 cc.). Titrate the solution with fiftieth-normal

sulfuric acid to a pink color, matched against a prepared blank. Each cubic centimeter of fiftieth-normal sulfuric acid is equivalent to 3.565 mg. of nikethamide. The amount of nikethamide found should be not less than 99 per cent nor more than 100.5 per cent.

**NITROFURAZONE.**— $C_6H_6O_4N_4$ .—M. W. 198.15.—5-Nitro-2-furfural semicarbazone.

Nitrofurazone occurs as an odorless, lemon-yellow colored crystalline powder, which turns brown-black and decomposes at from 236 to 240 C. It is nearly tasteless but develops a bitter after-taste. It is slightly soluble in alcohol (1:590), in propylene glycol (1:350) and in polyethylene glycol mixtures; very slightly soluble in water (1:4200); practically insoluble in ether. The crystals tend to darken on prolonged exposure to light. When dissolved in water, 1 mg. per 100 cc., nitrofurazone exhibits light absorption maximums in the ultraviolet region at 2600 Å and at 3750 Å, with a minimum of about 3060 Å.

Transfer about 1 Gm. of nitrofurazone to a stoppered cylinder and add 100 cc. of water. Shake the cylinder and contents for fifteen minutes and allow the solid to settle: the pH of the supernatant solution is in the range 6.0 to 6.5.

Place about 10 mg. of nitrofurazone in a test tube, add 5 cc. of water and 5 cc. of 10 per cent sodium hydroxide solution: the nitrofurazone dissolves and the solution is colored dark orange-red.

Place about 50 mg. of nitrofurazone in a 50 cc. flask, add 1 Gm. of granular zinc, 10 cc. of alcohol and 20 cc. of diluted sulfuric acid. Heat on a steam bath: the nitrofurazone dissolves slowly and the solution becomes practically colorless.

Dry about 0.5 Gm. of nitrofurazone, accurately weighed, at 100 C. for one hour: the loss in weight does not exceed 0.1 per cent.

Char about 0.5 Gm. of nitrofurazone, accurately weighed; cool, moisten with sulfuric acid and finally ignite: the residue does not exceed 0.05 per cent.

The nitrogen content of nitrofurazone, as determined by the Dumas micro-method, is not less than 28.1 per cent nor more than 28.6 per cent.

Weigh accurately about 10 mg. of nitrofurazone, transfer it to a 1 liter volumetric flask and dissolve the solid in about 50 cc. of aldehyde-free alcohol. Fill to the mark with water, mix and determine the optical density,  $E$ , of this solution and also that of several dilutions, such as  $\frac{3}{4}$ ,  $\frac{2}{3}$  and  $\frac{1}{2}$ , respectively, of the original concentration, at 3750 Å. Use a blank solution made by mixing 5 cc. of the aldehyde-free alcohol with 95 cc. of water. Calculate the  $E \frac{1\%}{1 \text{ cm.}}$  values for nitrofurazone from the data obtained. The observed values of  $E$  are a linear function of the concentration and the values of  $E \frac{1\%}{1 \text{ cm.}}$  calculated for each concentration average  $795 \pm 2\%$ .

**ORIDINE-Lilly.**—The calcium salt of the iodized fatty acids of cottonseed oil.

Oridine is a light brown powder, nearly odorless and tasteless. It is almost insoluble in water, benzene, ether and alcohol; and slightly soluble in chloroform and carbon tetrachloride.

Mix 1 Gm. of Oridine with 20 cc. of water and filter; the filtrate becomes but slightly opalescent on the addition of silver nitrate T.S. (*soluble iodides*).

Mix about 0.5 Gm. of Oridine, accurately weighed, in a nickel crucible with a mixture of four parts of powdered sodium hydroxide and one part of potassium nitrate and heat until fusion has been completed. Cool and dissolve the fused mass in 150 cc. of water, warming to hasten solution; filter into a 400 cc. beaker and wash well. Add 25 cc. of tenth-normal silver nitrate (the amount of silver is "k" in the formula below); then add slowly, with stirring, nitric acid until the solution is acid to litmus paper. Filter the solution through a weighed Gooch crucible, wash and titrate the excess silver nitrate in the filtrate with tenth-normal ammonia



thiocyanate (the amount of silver in the filtrate is "a"). The precipitate in the Gooch crucible (consisting mainly of silver iodide with some silver chloride) is further washed with 3 portions of alcohol, then ether, dried at 100° C. and weighed ("w"). The amount of iodine can be calculated according to the formula

$$x = \frac{.7527 w + a - k}{.293}$$

where w equals combined weight of silver iodide and silver chloride, x equals weight of silver iodide and (w-x) equals weight of silver chloride: by this method Oridine contains not less than 23 per cent nor more than 25 per cent of iodine. (Chlorine is used in the manufacture of Oridine so that the finished product contains from 1 to 3 per cent of combined chlorine.)

**ORTHOFORM.**— $C_8H_9NO_3$ .—M. W. 167.16.—The methyl ester of *m*-amino-*p*-hydroxybenzoic acid.

Orthoform occurs as a fine, white, crystalline powder, neutral in reaction, melting at from 141 to 143 C., odorless and tasteless. It is almost insoluble in water, freely soluble in alcohol and soluble in ether. It is decomposed, by boiling with water or by warming with alkalis or their carbonates, into methyl alcohol and *p*-hydroxy-*m*-aminobenzoic acid or its alkali salt. When crystallized from chloroform it sometimes assumes the form of white crystals, melting at from 110 to 111 C. and returning on melting to the ordinary form.

The filtrate obtained after shaking a small quantity of orthoform with water produces a transient color with ferric chloride T.S. and should not give a reaction with silver nitrate T.S. A solution of 0.1 Gm. of orthoform dissolved in 2 cc. of water by the aid of hydrochloric acid is colored yellowish red on the addition of 10 per cent sodium nitrite solution and then deposits a yellow precipitate, deepening to red on exposure to the air.

**OXIDIZED CELLULOSE.**— $(C_6H_8O_6)_n$ .—Absorbable cotton or gauze.—Cellulosic acid.

Oxidized cellulose, in the form of gauze or cotton, is slightly off-white in color, is acid to the taste and possesses a slight charred odor. It is soluble in dilute alkalis but insoluble in acids and water.

The solution obtained by vigorously shaking for one minute 0.2 Gm. of oxidized cellulose in 10 cc. of 1 per cent aqueous sodium hydroxide solution, followed by the addition of 10 cc. of water, shows only a few fibers or foreign particles and only a slight haze. The presence of some swollen fibers may be tolerated if such fibers disappear on standing for ten minutes. Addition of excess acid to the prepared solution causes a white, flocculent precipitate.

The moisture content of a 0.2 Gm. sample of oxidized cellulose, when dried in a vacuum over phosphorus pentoxide for 24 hours, does not exceed 15 per cent.

The residue on ignition of an accurately weighed specimen of oxidized cellulose does not exceed 0.15 per cent of the weight of the gauze or cotton.

Place 0.5 Gm. of oxidized cellulose, weighed to the nearest milligram, in a 125 cc. Erlenmeyer flask. Add 50 cc. of quarter-normal calcium acetate to the flask and swirl the contents until the sample is completely covered. Allow the mixture to stand for 30 minutes at room temperature, and titrate the solution with tenth-normal sodium hydroxide, using 5 drops of 5 per cent phenolphthalein T.S. as the indicator. Correct the titration by a blank run on 50 cc. of the calcium acetate solution. Each cc. of tenth-normal sodium hydroxide is equivalent to 0.0045 Gm. of carboxyl group. The carboxyl content is not less than 16 per cent nor more than 22 per cent, calculated on the dry basis.

Place a 1 Gm. sample of oxidized cellulose, weighed to the nearest milligram, in a 500 cc. Kjeldahl flask. Arrange a 125 cc. Erlenmeyer flask, containing 30 cc. of 4 per cent boric acid solution and 6 drops of mixed indicator (1 part of 0.1 per cent methyl red T.S. and 4 parts of 0.1 per cent bromocresol green T.S.), beneath the condenser of the

distillation apparatus so that the tip of the condenser is well below the surface of the boric acid solution. Add to the Kjeldahl flask containing the sample, 1 Gm. of Devarda's alloy (50 per cent copper, 45 per cent aluminum, and 5 per cent zinc), 100 cc. of ammonia-free distilled water, a small lump of paraffin wax, and 100 cc. of 5 per cent sodium hydroxide solution. Connect the Kjeldahl flask to the condenser by a suitable trap bulb. Heat the mixture in the flask until 45-50 cc. of distillate has collected in the receiver. Rinse the condenser and titrate the boric acid solution with tenth-normal sulfuric acid to a pale pink endpoint. Correct the titration by a blank run on the reagents in identical fashion. The nitrogen content should not be more than 0.5 per cent, calculated on the dry basis.

To 1 Gm. of oxidized cellulose in a 300 cc. Florence flask, add 120 cc. of one normal sulfuric acid and a few glass beads. Connect the reaction flask to an apparatus, arranged for distillation, with a dropping funnel filled with distilled water entering the flask. Transfer 10 cc. of a sodium bisulfite solution (13.7 Gm. of sodium bisulfite, or 12.5 Gm. of sodium metabisulfite per liter in water) into a receiver so that the condenser outlet is submerged in the bisulfite solution. The reaction flask is heated to boiling and during distillation, distilled water is added to the reaction flask from the dropping funnel at such a rate that the volume of the contents of the reaction flask is not appreciably altered. Carry on the distillation for one hour, collecting 250-300 cc. of distillate. Cool the distillate, if warm, and allow it to stand for 15 minutes to insure complete reaction of the bisulfite and formaldehyde. Add 1 cc. of starch T.S. and destroy the excess bisulfite by addition of tenth-normal iodine until a blue color is obtained. Discharge the blue color with a drop or two of tenth-normal sodium thiosulfate. Add 5 cc. of saturated sodium bicarbonate solution and titrate the liberated bisulfite with tenth-normal iodine. As the endpoint is approached, signaled by the very slow consumption of iodine, 0.5 cc. portions of half normal sodium carbonate are added, which discharge the blue color. The endpoint is reached when 1 cc. of the sodium carbonate solution does not discharge the blue color over a period of half an hour. Too great an excess of sodium carbonate is to be avoided since at high pH the iodoform reaction may take place with an increased consumption of iodine. Each cc. of tenth-normal iodine solution is equivalent to 1.5 mg. of formaldehyde. The formaldehyde content should not exceed 0.5 per cent of the weight of oxidized cellulose calculated on the dry basis.

**PAPAVERINE.**— $\text{C}_{20}\text{H}_{21}\text{NO}_4$ .—M. W. 339.38.—An alkaloid obtained from opium, belonging to the benzyl isoquinoline group (not a morphine derivative).

Papaverine occurs in fine, white rhombic prisms or needles or sometimes in scales: it is odorless and tasteless. It is nearly insoluble in cold water; slightly soluble in alcohol, ether, chloroform and benzene if cold and somewhat more soluble in these liquids when hot, but deposited by them on cooling; and soluble in warm petroleum ether and in acetone. It melts at  $147^\circ\text{C}$ .

If about 10 mg. of papaverine is dissolved in 10 cc. of water containing a few drops of diluted hydrochloric acid, and a few drops of potassium ferricyanide T.S. is added, a lemon yellow precipitate of papaverine ferricyanide should form at once (*distinction from other opium alkaloids*). If about 1 mg. of papaverine is dissolved in 0.1 cc. of sulfuric acid containing in each cubic centimeter 1 drop of formaldehyde solution, a colorless or, at most, a faintly yellowish-green solution should be produced. This gradually changes to deep rose and finally becomes brown (*distinction from morphine and its esters, which give purple or violet colors*). If 10 mg. of papaverine is dissolved in 0.2 cc. of sulfuric acid, the solution should not be colored more deeply than a very faint pink or brown (*limit of cryptopine, thebaine or of other organic impurities*). If 10 mg. of papaverine is dissolved in 10 cc. of water containing a few drops of hydrochloric acid, a few drops of a saturated aqueous solution of iodic acid added, and the mixture shaken with chloroform, the chloroform layer should not be colored violet (*morphine*).

If 0.2 to 0.3 Gm. of papaverine is weighed, dissolved in 20 cc. of warm water containing a few drops of diluted hydrochloric acid, the solution cooled, 1 cc. of freshly prepared potassium ferricyanide T.S. added, the mixture agitated, allowed to stand overnight and filtered, the filtrate made alkaline with ammonia water, shaken with several successive portions of ether, the ether solutions combined, washed with water, evaporated, the residue dried at 100 C. and weighed, the weight should not amount to more than 2 per cent of the weight taken (*limit of foreign opium alkaloids*).

**PARA-AMINOHIPPURIC ACID.**— $C_9H_{10}N_2O_3$ .—M. W. 194.19.—4-aminobenzoylglycine.—The N-acetic acid amide of *para*-aminobenzoic acid.

*Para*-aminohippuric acid occurs as a white, crystalline powder. It melts at 197.5° to 199° C. It is sparingly soluble in water and alcohol; and very slightly soluble in benzene, chloroform and ether.

Dissolve 0.1 Gm. of *p*-aminohippuric acid in 50 cc. of water. Add to 5 cc. of this solution 0.5 cc. of diluted hydrochloric acid and 0.5 cc. of 10 per cent sodium nitrite then add 10 cc. of diluted ammonia solution containing 0.2 Gm. of  $\beta$ -naphthol: a red color develops in the solution.

Place 50 mg. of *p*-aminohippuric acid in a test tube and add 0.5 cc. of potassium iodide T.S., followed by 2 cc. of water. Add 1 cc. of 5 per cent sodium hypochlorite solution: a red color develops in the solution (*distinction from p-aminobenzoic acid*).

Add 0.45 Gm. of *p*-aminohippuric acid, 0.2 Gm. of freshly fused sodium acetate, 0.25 Gm. of benzaldehyde and 0.75 Gm. of acetic anhydride to a 25 cc. Erlenmeyer flask. Place on a hot plate and shake the flask constantly until the material becomes liquid. Remove the flask immediately cool, suspend in 10 cc. of water and filter. Wash the crystals with about 10 cc. of alcohol and then with 10 cc. of ether: the dry crystals melt at 236° to 238° C.

Dissolve 1 Gm. of *p*-aminohippuric acid in a mixture of 10 cc. of normal sodium hydroxide and 40 cc. of distilled water. Add to 25 cc. of the solution 5 drops of freshly prepared sodium sulfide T.S. and acidify with 0.5 cc. of glacial acetic acid: no more darkening of the solution is produced than in that of a control to which 0.01 mg. of lead as lead nitrate has been added.

Render 10 cc. of the original solution slightly alkaline and pass hydrogen sulfide through it for ten minutes: no precipitate appears.

Add 30 cc. of distilled water and 5 cc. of normal hydrochloric acid to 5 cc. of the original solution: the solution shows no more sulfate than corresponds to 0.2 cc. of fiftieth-normal sulfuric acid, when treated by the U. S. P. test.

Dissolve 0.5 Gm. of *p*-aminohippuric acid in a mixture of 5 cc. of nitric acid and 15 cc. of distilled water: the solution shows no more chloride than corresponds to 0.1 cc. of fiftieth-normal hydrochloric acid when treated by the U. S. P. test.

Dry 0.25 Gm. of *p*-aminohippuric acid, accurately weighed, at 110° C. for two hours: the loss in weight does not exceed 0.25 per cent.

Ash about 0.25 Gm. of *p*-aminohippuric acid, accurately weighed: the amount of residue is not more than 0.05 per cent.

Weigh accurately about 2.5 Gm. of *p*-aminohippuric acid. Dilute to volume in a 250 cc. volumetric flask. Transfer 50 cc. of the solution to a 250 cc. beaker; add about 20 Gm. of ice and 5 cc. concentrated hydrochloric acid and allow to stand for about three minutes. Titrate the cooled solution with tenth-molar sodium nitrite solution previously standardized against sulfanilic acid, using an outside indicator of starch-iodide paste T.S. Each cc. of tenth-molar sodium nitrite is equivalent to 0.0194 Gm. of *p*-aminohippuric acid: the *p*-aminohippuric acid content is not less than 98 per cent and not more than 102 per cent.

**STERILE SOLUTION OF SODIUM PARA-AMINOHIPPURATE:** The pH of the ampul solution of sodium *p*-aminohippurate is not less than 7 or more than 7.6.

Dilute 10 cc. of the solution to volume in a 200 cc. volumetric flask. Transfer 50 cc. of the diluted solution to a 250 cc. beaker; and add about 20 Gm. of ice, 5 cc. of concentrated hydrochloric acid and allow to stand for about 3 minutes. Titrate the cooled solution with tenth-molar sodium nitrite previously standardized against sulfanilic acid, using an outside indicator of starch-iodide paste T.S. Each cc. of tenth-molar sodium nitrite is equivalent to 0.0194 Gm. of *p*-aminohippuric acid: the *p*-aminohippuric acid content is not less than 98 per cent or more than 102 per cent.

**PERCOMORPH LIVER OIL.**—*Oleum Percomorphum*.—A mixture containing the fixed oils obtained from the fresh livers of the percomorph fishes, principally *Xiphias gladius*, *Pneumatophorus diego*, *Thunnus thynnus* and *Stereolepis gigas*—sometimes also *Neothunnus macropterus*, *Katsuwonus pelamis*, *Sarda chiliensis*, *Germo alalunga*, *Thunnus orientalis*, *Scomber scombrus*, *Seriola dorsalis*, *Lutianus campechanus*, *Epinephelus morio*, *Roccus lineatus*, *Cynoscion nobilis*, *Eriscion macdonaldi*, *Epinephelus analogus*, *Stereolepis ishinagi* and *Sphyræna argentea*—containing not more than 50 per cent of other fish liver oil. It is biologically assayed and has a potency of not less than 60,000 units of vitamin A (U. S. P.) per gram and of not less than 8,500 units of vitamin D (U. S. P.) per gram.

Percomorph liver oil, 50%, in fish liver oil, is a yellow to brownish yellow, oily liquid. It has a slightly fishy but not rancid odor and a fishy taste. It is slightly soluble in alcohol, but is soluble in ether, chloroform, benzene, carbon disulfide and ethyl acetate. The specific gravity is from 0.0922 to 0.930 at 25° C. The refractive index is from 1.480 to 1.485 at 20° C.

A solution of one drop of the oil in 1 cc. of chloroform, when shaken with one drop of sulfuric acid, acquires a blue color, changing to violet, dark green, and finally brown. Treat 5 cc. of oil with 5 cc. of benzene and centrifuge for 25 minutes at 25° C.; no precipitate forms and a clear solution remains.

Fill a tall, cylindric, standard oil-sample bottle of about 120 cc. capacity with percomorph liver oil, 50%, in fish liver oil, at a temperature between 23 and 28° C., stopper, and immerse the bottle in a mixture of ice and distilled water for five hours: the oil remains fluid and forms no deposit.

Dissolve 2 Gm. of percomorph liver oil, 50%, in fish liver oil, in 20 cc. of a mixture of equal volumes of alcohol and ether, which previously has been neutralized with tenth-normal sodium hydroxide, using 5 drops of phenolphthalein T.S. as indicator, and titrate with tenth-normal sodium hydroxide to the production of a pink color which persists for fifteen seconds: not more than 1 cc. of tenth-normal sodium hydroxide is required (*free acid*). The amount of unsaponifiable matter as determined by the method of U. S. P. XIII, p. 648, is not less than 3.5 per cent nor more than 7 per cent; it is semisolid in appearance. The saponification value as determined by the method of U. S. P. XIII, p. 647, is not less than 174 and not more than 186. The iodine value as determined by the method of U. S. P. XIII, p. 647, on 0.18 to 0.20 Gm. of sample, accurately weighed, is not less than 145 and not more than 180.

**UNDILUTED PERCOMORPH LIVER OIL:** The undiluted fixed oil obtained from the fresh livers of the percomorph fishes and used in the preparation of percomorph liver oil, 50%, in fish liver oil, conforms to the following constants as determined by methods of U. S. P.: specific gravity, from 0.924 to 0.930 at 25° C.; refractive index, from 1.484 to 1.490 at 20° C.; free acid in 2 Gm., equivalent to not more than 1 cc. of tenth-normal sodium hydroxide; unsaponifiable matter, not less than 7 nor more than 13 per cent (semisolid in appearance); saponification value, not less than 168 nor more than 182; iodine value, not less than 145 nor more than 180.

**PHENARSONE SULFOXYLATE.**— $C_7H_8AsNNa_2O_6S$ .—M. W. 355.11.—Sodium 3-amino-4-hydroxyphenylarsonate-N-methanal sulfoxylate.

Phenarsone sulfoxylate occurs as a white, odorless, amorphous powder. It is soluble in water, dilute acids, alkalis and alkali carbonates; slightly soluble in methyl alcohol; and insoluble in ether and alcohol. The  $pH$  of a 5 per cent solution is from 7.0 to 7.4.

Add 0.2 Gm. of sodium hydrosulfite to about 0.1 Gm. of phenarsone sulfoxylate dissolved in 5 cc. of water and warm at 50-60 C. for five minutes: a yellow solution is produced. Add normal hydrochloric acid dropwise to the solution: a lemon-yellow gelatinous precipitate forms, soluble in excess hydrochloric acid. Add 1 cc. of iodine solution and 2 cc. of chloroform to 10 cc. of a 1 per cent solution of phenarsone sulfoxylate; shake the test tube and contents and then allow the liquids to separate: no color appears in either of the liquid layers. Repeat the test, first adding 0.25 Gm. of sodium bicarbonate: no color appears in the chloroform layer, but the aqueous layer is colored light brown. Add 2 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. to 5 cc. of a 1 per cent solution of phenarsone sulfoxylate: a black precipitate forms. Heat to boiling and cool: the mixture rapidly changes to a yellow-brown solution containing a white precipitate. Decant the solution: the precipitate is soluble in excess strong ammonia solution. Add 3 drops of alkaline mercuric potassium iodide T.S. to 5 cc. of a 1 per cent solution of phenarsone sulfoxylate: a gray to black precipitate of metallic mercury is formed (*distinction from acetarsone, tryparsamide and other pentavalent arsenicals*).

Dissolve 0.1 Gm. of phenarsone sulfoxylate in 5 cc. of water, add 0.5 cc. of a 10 per cent sodium nitrite solution, cool in ice water and add 0.1 cc. of 10 per cent hydrochloric acid followed by 0.1 cc. of a solution containing 5 per cent beta-naphthol and 10 per cent sodium hydroxide solution: no red color is produced on standing (*absence of 3-amino-4-hydroxyphenyl-arsonic acid*).

Dissolve 0.5 Gm. of phenarsone sulfoxylate in 10 cc. of water, add 1 cc. of diluted ammonia solution and 1 cc. of magnesia mixture: no precipitate forms (*absence of inorganic arsenate*). Heat the solution to boiling: a white precipitate forms slowly.

Dry an accurately weighed 1 Gm. portion of phenarsone sulfoxylate, contained in a weighing bottle not less than 20 mm. in diameter, over fresh phosphorus pentoxide for twenty-four hours in a vacuum of at least 5 mm. of mercury: the loss in weight is not more than 2.5 per cent. Transfer about 0.5 Gm. of phenarsone sulfoxylate accurately weighed to a tared porcelain dish, add 0.5 cc. of sulfuric acid and gently ignite. Cool, treat the ash with 5 drops of sulfuric acid and 5 drops of hydrochloric acid. Evaporate the acids over a low flame and then ignite, cool and weigh: the weight of the sulfated residue is equivalent to a sodium content of not less than 15.2 per cent nor more than 16.2 per cent. The residue responds to tests for sodium.

Dissolve about 0.5 Gm. of phenarsone sulfoxylate, accurately weighed, in 25 cc. of water; add 10 cc. of silver nitrate T.S. and 10 cc. of nitric acid. Warm on a steam bath for 15 minutes and finally add 100 cc. of water. Continue the digestion on the steam bath for 30 minutes, cool, allow to stand 30 minutes and collect the precipitated silver chloride on a suitable tared sintered glass filter (or Gooch crucible). Wash the precipitate and dry at 100 C. for one hour: the weight of silver chloride found is equivalent to a chlorine content of not less than 6.5 per cent nor more than 7.5 per cent.

Dissolve about 0.5 Gm. of phenarsone sulfoxylate in 10 cc. of water contained in a 400 cc. beaker and add a solution made by dissolving carefully 5 Gm. of sodium peroxide in 25 cc. of water. Cover the beaker with a watch glass and heat on a steam bath for one hour. Cool, add hydrochloric acid down the side of the beaker with stirring until the solution is colorless and then add 1 cc. in excess. Add 25 cc. of water and boil the solution gently, covering the beaker with a watch glass, until the volume is reduced by one half. Dilute to approximately 300 cc. with water, boil and add 15 cc. of barium chloride T.S., dropwise at first, until the precipitate forms. Digest the mixture for one hour on the steam bath and

filter while hot, collecting the precipitated barium sulfate on a suitable tared, previously ignited, Gooch crucible. Wash the precipitate with hot water until chlorides are absent from the washings. Dry the crucible and contents at  $100^{\circ}\text{C}$ . for 15 minutes and finally ignite at  $650^{\circ}\text{C}$ . for 15 minutes: the weight of barium sulfate formed is equivalent to a sulfur content of not less than 6.5 per cent nor more than 7.5 per cent.

Transfer about 0.5 Gm. of phenarsone sulfoxylate, accurately weighed, to a 250 cc. wide mouthed Erlenmeyer flask, add 10 cc. of water to dissolve the sample taken and then add 15 cc. of 30 per cent hydrogen peroxide. Mix and add 10 cc. of sulfuric acid slowly down the side of the flask, shaking the mixture after each addition. Place a short stemmed funnel in the top of the flask and heat at medium temperature until the reaction subsides. Remove the funnel and heat for twenty minutes at a temperature such as to produce sulfur trioxide fumes freely. (If at the end of five minutes the solution is not colorless, cool and add from 2 to 5 cc. of 30 per cent hydrogen peroxide, then continue to heat as before.) Cool and add through a long stemmed funnel 0.2 Gm. of hydrazine sulfate (*chlorine free*). (*Care should be taken to prevent adherence of hydrazine sulfate to the wall of the flask.*) Heat the acid solution to dissolve any crystals of hydrazine sulfate and then heat sufficiently for 20 minutes to produce fumes of sulfur trioxide, which partially condense at a point about 2 inches from the top of the flask. Cool, dilute (*carefully*) with 20 cc. of distilled water, add from 3 to 5 drops of a methyl orange solution (3 cc. of methyl orange T.S. diluted to 100 cc. with water) and titrate while hot with tenth-normal potassium bromate until the solution becomes colorless. Near the end point the potassium bromate should be added dropwise. Each 1 cc. of tenth-normal potassium bromate is equivalent to 0.003746 Gm. of arsenic: the amount of arsenic found is not less than 17.0 per cent nor more than 18.5 per cent.

**PHENETSAL.**— $\text{C}_{15}\text{H}_{13}\text{NO}_4$ .—M. W. 271.26.—Acetyl-*p*-aminophenyl salicylate.

Phenetsal forms small, white crystalline leaflets or powder, odorless and tasteless, melting at from  $187$  to  $188^{\circ}\text{C}$ . It is almost insoluble in cold water, more soluble in warm water, freely soluble in aqueous solutions of alkalis and in alcohol, ether and benzene, but not in petroleum benzene.

If its alkaline solution is boiled, it gradually becomes blue; on continuing the boiling the color is discharged, but is again produced on cooling and exposure to air. On the addition of ferric chloride to the alkaline solution, the violet color characteristic of salicylic acid is produced, but a simple aqueous solution of phenetsal does not react with ferric chloride and should not be changed by silver nitrate T.S. It forms a colorless solution with concentrated sulfuric acid.

It is incompatible with alkalis, which decompose it.

**PHENOLTETRACHLOROPHTHALEIN.**— $\text{C}_{20}\text{H}_8\text{Cl}_4$   
 $\text{O}_4$ .—M. W. 454.09.

Phenoltetrachlorophthalein is a cream white powder; odorless; stable in the air. It is practically insoluble in water; very soluble in acetone; soluble in alcohol, ether and glacial acetic acid; and slightly soluble in chloroform, benzene and carbon disulfide. It dissolves in solutions of the alkalis and carbonates to form solutions which are deep purple when concentrated, but which change to violet-red on dilution, and in very dilute solutions assume a bluish tint (*distinction from phenolphthalein*).

Phenoltetrachlorophthalein does not melt when heated to  $300^{\circ}\text{C}$ . It does not respond to the U. S. P. test for heavy metals as described under phenolphthalein.

Dry about 1 Gm. of phenoltetrachlorophthalein, accurately weighed, to constant weight at  $115^{\circ}\text{C}$ .: the loss is not more than 0.5 per cent. To about 5 Gm. of the substance, accurately weighed, add 25 cc. of normal sodium hydroxide solution, heat to about  $70^{\circ}\text{C}$ . and stir. Dilute with warm water to about 75 cc., filter through a tared Gooch crucible, dry to constant weight at  $115^{\circ}\text{C}$ . and weigh: the weight of the insoluble matter (*tetrachlorofluorane*) does not exceed 0.2 per cent. Ignite about 2 Gm. of the substance, accurately weighed: the ash does not exceed 0.15 per cent.

**PHENTETIOTHALEIN SODIUM.**— $C_{22}H_{18}I_4Na_2O_4$ .—M. W. 889.96.—Phenoltetraiodophthalein Sodium.

Phentetiothalein sodium occurs as bronze purple, odorless, slightly hygroscopic granules. It is soluble in water and alcohol.

Dissolve 1.0 Gm. of phentetiothalein sodium in 10 cc. of water: a clear solution results. Add diluted hydrochloric acid drop by drop to 1 cc. of a 10 per cent aqueous solution of phentetiothalein sodium: a yellow colored precipitate appears. Add sodium hydroxide solution in large excess to 1 cc. of a 10 per cent aqueous solution of phentetiothalein sodium: a permanent purple color appears.

Intimately mix 0.1 Gm. of the salt with 1.0 Gm. of anhydrous sodium carbonate and heat to fusion; cool the mixture, dissolve in diluted hydrochloric acid and filter; add a few drops of 3 per cent hydrogen peroxide solution and agitate the mixture with a few cc. of chloroform: the chloroform layer is colored violet (*iodine*).

Transfer about 0.5 Gm., accurately weighed, of phentetiothalein sodium to a flat type weighing bottle and dry in a vacuum at 80 C. to constant weight: the loss in weight is not more than 5 per cent.

Run a Carius determination on about 0.2 Gm., accurately weighed, of phentetiothalein sodium: the amount of iodine found is not less than 56 per cent nor more than 59 per cent when calculated to the dry basis.

**PHENYLEPHRINE HYDROCHLORIDE.**— $C_9H_{11}ClNO_2$ .—M. W. 203.67.—1-(*m*-Hydroxyphenyl)-2-methylamino-ethanol hydrochloride.

Phenylephrine hydrochloride occurs as white, odorless, nonhygroscopic crystals possessing a bitter taste. It is readily soluble in water and alcohol. The aqueous solution is neutral to litmus paper. It melts between 139° and 143° C.

Transfer 0.3 Gm. of phenylephrine hydrochloride to a glass container, dissolve in 3 cc. of water, add 15 drops of diluted ammonia solution and rub the glass container with a glass rod: the base that separates when washed with cold water and dried melts at 170-171° C., without decomposition. Determine the nitrogen content of the base by the micro Dumas method: the nitrogen found is not less than 8.2 per cent nor more than 8.5 per cent. Dissolve 10 mg. of phenylephrine hydrochloride in 1 cc. of water and add 1 cc. of cupric sulfate T.S. followed by 1 cc. of 20 per cent sodium hydroxide solution: a reddish purple color forms that is not extracted by ether. Dissolve 10 mg. of phenylephrine hydrochloride in 1 cc. of water and add 1 drop of ferric chloride T.S.: a permanent amethyst purple color develops. Dissolve 20 mg. of phenylephrine hydrochloride in 3 cc. of alcoholic potassium hydroxide T.S., add 3 drops of chloroform and boil: there is no odor of carbylamine (*absence of primary amines*). Dissolve 50 mg. of phenylephrine hydrochloride in 30-40 cc. of distilled water, add 1 cc. of diluted hydrochloric acid in 1 cc. of barium chloride T.S.: no turbidity should result (*absence of sulfate*). Dissolve 0.2 Gm. of phenylephrine hydrochloride in 10 cc. of distilled water: the solution yields a negative test for heavy metals when tested according to the U. S. P. method (see U. S. P. XIII, p. 657). To 1 cc. of a solution containing 0.2 Gm. of phenylephrine hydrochloride add 2 drops of a freshly prepared 1 per cent sodium nitroprusside solution, then 1 cc. of sodium hydroxide T.S. followed by 0.6 cc. (10 drops) of glacial acetic acid: the final solution should not be a deeper yellow than the same reagents, without the phenylephrine hydrochloride (*absence of corresponding ketone*).

Heat about 0.2 Gm. of phenylephrine hydrochloride, accurately weighed, for twenty-four hours, in an oven at 100° C.: the loss is not more than 1 per cent.

Dissolve about 0.2 Gm. of phenylephrine hydrochloride, accurately weighed, in 200 cc. of water, heat to boiling, add 4 cc. of diluted nitric acid, followed by silver nitrate T.S. in slight excess; allow the container and mixture to stand for six hours, transfer to a Gooch crucible, wash well with diluted nitric acid (10 cc. of diluted nitric acid diluted to 100 cc.), dry at 100° C. cool in a desiccator and weigh: the chlorine

calculated from the silver chloride weighed is not less than 17.20 per cent nor more than 17.70 per cent. Determine the nitrogen content by the micro Dumas method: the nitrogen found is not less than 6.6 per cent nor more than 7.0 per cent.

Transfer about 0.5 Gm. of phenylephrine hydrochloride, accurately weighed, to a platinum dish; ignite until constant weight is attained: the ash is less than 0.2 per cent.

**PHENYLEPHRINE HYDROCHLORIDE ONE PER CENT SOLUTION:** Transfer 10 cc. of the solution to a beaker, evaporate the solution to dryness on a boiling water bath, extract the residue with three 15 cc. portions of boiling absolute isopropyl alcohol, evaporate the isopropyl alcohol to dryness on a boiling water bath, dry the extract in an oven at 100° C. to constant weight: the residue is equal to not less than 0.95 per cent nor more than 1.05 per cent. The melting point of the residue is between 138° and 142° C.

Dissolve the residue in 3 cc. of water, add 10 drops of diluted ammonia solution, rub the glass container with a glass rod, filter the precipitate, wash with cold water on a porous plate: the melting point of the phenylephrine base is 169-171° C.

**PHENYLEPHRINE HYDROCHLORIDE ¼ PER CENT SOLUTION:** Follow the assay procedure described for the 1 per cent solution except use a 25 cc. sample.

### PHENYLMERCURIC BORATE TINCTURE 1:500.

—A tincture consisting of acetone 4.6 per cent, alcohol 43.2 per cent and water 50 per cent, containing phenylmercuric borate ( $C_6H_5BHgO_2 \cdot H_2O$ .—M. W. 338.55) 0.2 per cent, with 1.0 per cent each of boric acid and sodium acid phosphate.

Phenylmercuric borate tincture 1:500 is a colorless solution which possesses the odor of acetone and alcohol and a *pH* value of about 5.7. Its specific gravity is between 0.920 and 0.940 at 25° C.

To 2 cc. of phenylmercuric borate tincture 1:500 add 2 cc. of water and 2 drops of 1 per cent sodium chloride solution: a white precipitate which is soluble in sodium hydroxide and may be reprecipitated by the addition of nitric acid is formed. To 10 cc. of phenylmercuric borate tincture 1:500 add 2 cc. of saturated sodium chloride solution: a precipitate forms. Filter, wash the precipitate with cold water, and dry it on a porous plate: the melting point of the phenylmercuric chloride is between 248° and 255° C. Evaporate 5 cc. of phenylmercuric borate tincture 1:500 on a water bath, cool, add 2 cc. of methyl alcohol, ignite the solution: the flame is green. To 2 cc. of phenylmercuric borate tincture 1:500 add 2 cc. of water and 1 cc. of silver nitrate T.S.: a yellow precipitate forms, soluble in nitric acid.

To 2 cc. of phenylmercuric borate tincture 1:500 add 2 cc. of water followed by 2 cc. of potassium iodide T.S., added a drop at a time: a white precipitate forms in the solution that at no time shows traces of orange or red and is insoluble in the excess of potassium iodide (*mercuric ions*). To 2 cc. of phenylmercuric borate tincture 1:500 add 2 cc. of water and 2 cc. of sodium hydroxide T.S.: the solution remains clear and does not blacken (*mercurous ions*). To 3 cc. of phenylmercuric borate tincture 1:500 add 5 cc. of sulfuric acid, cool, overlay with fresh saturated solution of ferrous sulfate: a brown ring does not appear (*nitrate*).

Transfer 25 cc. of phenylmercuric borate tincture 1:500, accurately measured, to a suitable flask; add 25 cc. of water, 10 cc. of ferric ammonium sulfate T.S. and 5 cc. of nitric acid. Titrate, using fiftieth-normal ammonium thiocyanate delivered from a 10 cc. buret, until the color of the solution matches that of a control containing 50 cc. of water, 10 cc. of ferric ammonium sulfate T.S., 5 cc. of nitric acid and 0.10 cc. of fiftieth-normal ammonium thiocyanate. Subtract 0.10 cc. from the volume noted in the titration; the volume difference is equivalent to not less than 37.5 mg. nor more than 42.5 mg. of phenylmercuric ion ( $C_6H_5Hg^+$ ). Each cubic centimeter of fiftieth-normal ammonium thiocyanate is equivalent to 5.554 mg. of phenylmercuric ion.



**PHENYLMERCURIC PICRATE TINCTURE 1:200 WITH PICRIC ACID.**—A tincture consisting of acetone 10 per cent, alcohol 50 per cent and water 38.3 per cent, containing phenylmercuric picrate ( $C_{12}H_7HgN_3O_7$ .—M. W. 505.82) 0.5 per cent with picric acid (trinitrophenol) 1.2 per cent.

Phenylmercuric picrate tincture 1:200 with picric acid is a strongly yellow colored solution which possesses the odor of acetone and alcohol and a pH value of about 2.0. Its specific gravity is between 0.898 and 0.901 at 25° C.

To 2 cc. of phenylmercuric picrate tincture 1:200 add 2 cc. of water and 2 drops of 1 per cent sodium chloride solution: a white precipitate, which is soluble in sodium hydroxide and may be reprecipitated by the addition of nitric acid, is formed. To 10 cc. of phenylmercuric picrate tincture 1:200 add 2 cc. of saturated sodium chloride solution: a precipitate forms. Filter, wash the precipitate with cold water, and dry it on a porous plate: the melting point of the phenylmercuric chloride is between 248° and 255° C.

To 5 cc. of phenylmercuric picrate tincture 1:200 add 5 cc. of water and 2 cc. of diluted nitric acid; extract the solution with three 10 cc. portions of ether; combine the ether extracts, filter through a cotton pledget and evaporate the ether: the picric acid obtained melts (*Caution!*) from 120° to 123° C.

To 2 cc. of phenylmercuric picrate tincture 1:200 add 2 cc. of water followed by 2 cc. of potassium iodide T.S. added a drop at a time: a white precipitate forms in the yellow solution that at no time shows traces of orange or red color and is insoluble in the excess of potassium iodide (*mercuric ions*). To 2 cc. of phenylmercuric picrate tincture 1:200 add an excess of sodium hydroxide T.S.: the solution becomes orange-red, but there is no precipitate and the solution does not blacken (*mercurous salts*). To 3 cc. of phenylmercuric picrate tincture 1:200 add 5 cc. of sulfuric acid, cool, overlay with a saturated solution of ferrous sulfate: a brown ring does not appear (*nitrate*).

The mercury content of phenylmercuric picrate tincture 1:200 can be determined by a suitable electrolytic method: the mercury content is equivalent to not less than 0.26 per cent nor more than 0.28 per cent calculated as phenylmercuric ion. The phenylmercuric ion content also may be determined, as directed under phenylmercuric borate tincture 1:500, after removal by ether extraction of the picric acid from a portion of the tincture acidified with nitric acid.

*Caution:* Phenylmercuric picrate tincture 1:200 with picric acid is more subject to decomposition on aging than certain other phenylmercuric salts.

**PHENYLPROPANOL AMINE HYDROCHLORIDE.**— $C_9H_{14}ClNO$ .—M. W. 187.67.—*d*, 1-1-Phenyl-2-aminopropanol hydrochloride.

Phenylpropanol amine hydrochloride occurs as a white, crystalline powder, possessing an odor resembling that of benzoic acid. It is freely soluble in water and alcohol; insoluble in ether, chloroform and benzene. Its aqueous solution is neutral to litmus. Phenylpropanol amine hydrochloride melts at 190-194° C.

Dissolve about 0.5 Gm. of phenylpropanol amine hydrochloride in 25 cc. of water and add 5 cc. of a saturated solution of sodium carbonate. Cool in an ice bath and collect the resultant needle-shaped crystals on a filter paper, wash and dry at 80° C.: the melting point of the  $\alpha$ -hydroxy- $\beta$ -amino-propylbenzene is 101-101.5° C.

Dissolve 0.05 Gm. of phenylpropanol amine hydrochloride in 100 cc. of water: separate portions of 2 cc. yield a yellow color with 5 drops of ferric chloride T.S. (*distinction from Cobefrin and epinephrine*); no precipitate with mercuric potassium iodide T.S. (*distinction from amphetamine*). To about 0.1 Gm. of phenylpropanol amine hydrochloride in 5 cc. of water, add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride T.S.: no turbidity develops (*sulfate*).

Dry about 0.3 Gm. of phenylpropanol amine hydrochloride, accurately weighed, to constant weight at 100° C.: the loss in weight does not

exceed 1 per cent. Incinerate about 0.3 Gm. of phenylpropanol amine hydrochloride, accurately weighed: the residue does not exceed 0.3 per cent. Transfer about 0.2 Gm. of phenylpropanol amine hydrochloride, accurately weighed, to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the method described in *Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, page 26, paragraph 24: the amount of nitrogen is not less than 7.34 per cent, nor more than 7.52 per cent when calculated to the dried substance. Transfer about 0.2 Gm. of phenylpropanol amine hydrochloride, accurately weighed, to a 400 cc. beaker and determine the chlorine content according to the method as described in *Methods of Analysis A. O. A. C.*, ed. 6, page 128, paragraph 42: the amount of chlorine found corresponds to not less than 18.85 per cent, nor more than 19.95 per cent when calculated to the dried substance.

**PHENYLPROPYLMETHYL AMINE.**— $C_{10}H_{15}N$ .—  
M. W. 149.23.—*d,l*-1-Methylamino-2-phenylpropane.

Phenylpropylmethyl amine occurs as a colorless to pale yellow liquid which exhibits an initial boiling point of  $203^{\circ}C$ , with 98 per cent of the sample distilling from  $205^{\circ}$  to  $210^{\circ}C$ .

At  $25^{\circ}C$ . phenylpropylmethyl amine has a vapor pressure of less than 1.0 mm., a specific gravity of from 0.915 to 0.925 and a refractive index of 1.507 to 1.511. It is slightly soluble in water (1.2 Gm. per 100 cc.) but very soluble in alcohol, benzene and ether. Aqueous solutions of phenylpropylmethyl amine are alkaline to litmus; the pH of a solution of 2 drops (about 0.1 cc.) of phenylpropylmethyl amine diluted with 10 cc. of water is about 10.5.

Dissolve 0.5 cc. of phenylpropylmethyl amine in 10 cc. of dry benzene and bubble hydrogen chloride, dried by passage over calcium chloride, through the solution until precipitation occurs. Filter and recrystallize the phenylpropylmethyl amine hydrochloride from hot benzene. Wash the recrystallized product with dry benzene followed by dry ether, and finally air-dry the crystals by suction: the phenylpropylmethyl amine hydrochloride melts at  $144-148^{\circ}C$ .

Transfer about 0.5 cc. of phenylpropylmethyl amine, accurately weighed, to a tared, low form, weighing bottle. Evaporate on a steam bath to constant weight: the nonvolatile matter does not exceed 0.5 per cent.

Dissolve 0.5 cc. of phenylpropylmethyl amine in 10 cc. of 10 per cent nitric acid and add 1 cc. of silver nitrate T.S.: no more chloride is present than appears with a control containing 0.4 cc. of one-hundredth normal hydrochloric acid.

Add 1 drop of phenylpropylmethyl amine to 2 cc. of alcohol. Place 1 drop of the resulting solution in a test tube with 1 drop of chloroform and 5 cc. of 10 per cent sodium hydroxide solution; heat gently: no odor of isocyanide is detectable.

Transfer a portion of phenylpropylmethyl amine (0.5 to 1.0 Gm.), accurately weighed, to a 50 cc. volumetric flask, add neutral 50 per cent alcohol to the mark and mix. To 10 cc. aliquots of the solution add 20 cc. of tenth-normal sulfuric acid and back-titrate the excess acid with tenth-normal sodium hydroxide, using methyl red T.S. as the indicator. Each cc. of tenth-normal sulfuric acid is equivalent to 0.0149 Gm. of phenylpropylmethyl amine: the phenylpropylmethyl amine content is not less than 96.0 per cent nor more than 101.0 per cent.

**PHENYLPROPYLMETHYL AMINE INHALER:** Transfer the wick of the inhaler to a 500 cc. Kjeldahl flask. Rinse the inhaler case with small amounts of alcohol, adding the washings to the flask by means of a small funnel. Add 250 cc. of water and 1.0 Gm. of sodium hydroxide; immediately connect the flask to the ammonia distillation apparatus and boil the contents of the flask to distil the volatile base into 30 cc. of tenth-normal hydrochloric acid. Distil approximately 150 cc. of liquid, rinse the condenser with water and titrate the solution in the receiving flask with tenth-normal sodium hydroxide, using methyl red T.S. as the indicator. Each cc. of tenth-normal acid is equivalent to 0.0149 Gm. of phenylpropylmethyl amine: the amount of phenylpropylmethyl amine found is not less than 0.250 Gm. per inhaler.

**PHTHALYLSULFATHIAZOLE.**— $C_{17}H_{13}O_5N_3S_2$ .—M. W. 403.42.—2-(N-phthalylsulfanilamido)thiazole.

Phthalylsulfathiazole occurs as an odorless, white or faintly yellowish white, crystalline powder possessing a slightly bitter taste. It may slowly darken on long exposure to light. It is slightly soluble in alcohol; very slightly soluble in ether; and practically insoluble in chloroform and water; it is readily soluble in sodium or potassium hydroxide solution, diluted ammonia solution and concentrated hydrochloric acid.

Phthalylsulfathiazole darkens and effervesces at  $244^{\circ}$  to  $250^{\circ}$  C. and melts from  $272^{\circ}$  to  $277^{\circ}$  C., with decomposition, when the melting point bath is preheated to about  $220^{\circ}$  to  $225^{\circ}$  C. before immersion of the sample tube.

Place about 0.25 Gm. of phthalylsulfathiazole in a test tube and add 5 cc. of 10 per cent sodium bicarbonate solution. The substance dissolves on warming and carbon dioxide is evolved (*distinction from sulfanilamide, sulfathiazole, sulfapyridine, sulfaguanidine and sulfadiazine*).

Add 10 cc. of concentrated hydrochloric acid to about 0.5 Gm. of phthalylsulfathiazole contained in a small beaker, cover with a watch glass and heat on a steam bath until the solid has nearly all dissolved. Cool the solution, transfer to a separatory funnel and extract with two 25 cc. portions of ether, combine the extracts and evaporate to dryness: the melting point of the residue is not less than  $195^{\circ}$  C.

Digest 2.0 Gm. of phthalylsulfathiazole with 100 cc. of distilled water at room temperature for 30 minutes; filter. (1) To 25 cc. of filtrate add two drops of phenolphthalein T.S. and titrate with tenth-normal sodium hydroxide: not more than 1 cc. of the sodium hydroxide solution is required to produce a pink color. (2) To another 25 cc. of the filtrate add 1 cc. of nitric acid and 1 cc. of silver nitrate T.S.: mix well and allow to stand for five minutes protected from direct sunlight: the turbidity does not exceed that produced in a control test made with 0.1 cc. of fiftieth-normal hydrochloric acid. (3) To another 25 cc. of the filtrate add 1 cc. of diluted hydrochloric acid and 1 cc. of barium chloride T.S.; mix well and allow to stand for ten minutes: the turbidity does not exceed that produced in a control test made with 0.2 cc. of fiftieth-normal sulfuric acid.

Dissolve 0.5 Gm. of phthalylsulfathiazole in a mixture of 5 cc. of one-normal sodium hydroxide and 20 cc. of distilled water: the solution is clear and not more than pale yellow; add five drops of freshly prepared 10 per cent sodium sulfide solution: the darkening produced does not exceed that developed in a control test to which has been added 0.01 mg. of lead.

Dry an accurately weighed sample of phthalylsulfathiazole at  $100^{\circ}$  C. for 24 hours: the loss in weight does not exceed 2.0 per cent.

Ignite about 1 Gm. of phthalylsulfathiazole, accurately weighed. Cool, add sufficient sulfuric acid to moisten the charred mass and ignite to constant weight: the ash is not more than 0.1 per cent.

Accurately weigh about 1 Gm. of phthalylsulfathiazole, previously dried at  $100^{\circ}$  C., for four hours. Transfer the weighed sample to a 250 cc. beaker and add 20 cc. of hydrochloric acid. Cover with a watch glass and heat on a water bath for two hours. Filter the mixture into a separatory funnel. Wash the beaker and the filter paper with several portions of 10 per cent hydrochloric acid, collecting the washings in the separatory funnel. Extract the cool filtrate with five 50 cc. portions of ether, discarding the ether extracts. Heat the aqueous solution on a water bath until all of the ether is driven off. Add 5 cc. of concentrated hydrochloric acid, cool to  $15^{\circ}$  C. and slowly titrate with one-tenth molar sodium nitrite, stirring vigorously, until a blue color is produced immediately when a glass rod dipped into the titrated solution is streaked on a smear of starch-iodide paste T.S. When the titration is complete, the end point is reproducible after the mixture has been allowed to stand for one minute. Each cc. of one-tenth molar sodium nitrite is equivalent to 0.04034 Gm. of phthalylsulfathiazole: the amount of phthalylsulfathiazole found corresponds to not less than 96 per cent nor more than 102 per cent.

**POTASSIUM SODIUM BISMUTHYL TARTRATE.**

—A basic water soluble potassium sodium bismuth tartrate containing from 40.75 to 41.25 per cent of bismuth.

Potassium sodium bismuthyl tartrate is a white, heavy powder, soluble in water and insoluble in organic solvents.

During the ignition of about 1 Gm. of potassium sodium bismuthyl tartrate in a quartz crucible, a small globule of metallic bismuth forms that oxidizes on extended heating. The residue is yellow and alkaline to litmus, and effervesces with acids.

Transfer 0.1 Gm. of potassium sodium bismuthyl tartrate to a test tube, add 5 cc. of water and sufficient diluted hydrochloric acid to dissolve the precipitate first formed and add 0.5 cc. of barium chloride T.S.: no cloudiness appears within 2 minutes.

Transfer 0.1 Gm. of potassium sodium bismuthyl tartrate to a test tube, add 5 cc. of water and sufficient diluted nitric acid to dissolve the precipitate first formed and add 0.5 cc. of silver nitrate T.S.: no precipitate appears.

A sample of potassium sodium bismuthyl tartrate loses not more than 0.3 per cent of its weight when dried in a vacuum over sulfuric acid.

Transfer about 0.5 Gm. of potassium sodium bismuthyl tartrate, accurately weighed, to an Erlenmeyer flask; add 100 cc. of water, diluted hydrochloric acid, a drop at a time, until the precipitate that forms redissolves; saturate the solution with hydrogen sulfide and filter; wash successively with water, alcohol, chloroform and ether; dry at 100° C.; cool in a desiccator and weigh: the bismuth sulfide weighed is equivalent to not less than 40.75 per cent nor more than 41.25 per cent of bismuth.

**PROBARBITAL CALCIUM.**— $C_{18}H_{26}CaN_4O_6 \cdot 3H_2O$ .—M. W. 488.58.—The trihydrated calcium salt of 5-ethyl-5-isopropyl barbituric acid.

Probarbital calcium occurs as a white, crystalline, odorless powder, with a slightly bitter taste. It is soluble in about 40 parts of water at 25° C.; and insoluble in alcohol. An aqueous solution is alkaline to litmus. Add 0.2 Gm. to 20 cc. of water, acidify with 5 cc. diluted hydrochloric acid, filter, make the filtrate ammoniacal, and add 2 cc. of ammonium oxalate T.S.: a precipitate forms, insoluble on addition of 36 per cent acetic acid in excess, but soluble on the addition of hydrochloric acid. Wash the residue from the foregoing thoroughly with water and dry at 100° C.: the melting point should be from 200° to 203° C. To 0.05 Gm. of residue add 2 cc. sodium hydroxide T.S.: the residue dissolves. Place 2 Gm. in a glass stoppered flask, treat with 25 cc. of carbon dioxide-free water and agitate occasionally over a period of two hours; by decantation separate the insoluble material, transfer the insoluble residue to a test tube, treat it with diluted sulfuric acid and pass the emitted gases into 20 cc. of barium hydroxide solution: not more than a barely perceptible turbidity should result (*limit of carbonate*). Dry about 1 Gm., accurately weighed, to constant weight at 100° C.: the loss does not exceed 12 per cent. Transfer about 1 Gm., accurately weighed, to a glass stoppered cylinder, add 50 cc. of ether, stopper and shake the contents for five minutes; decant the supernatant liquid through filter paper and repeat, using 25 cc. and 15 cc. portions, respectively, of ether; evaporate the filtrate to dryness in a tared beaker and dry to constant weight at 100° C.: the residue should not weigh more than 4 per cent (*limit of uncombined ethylisopropyl barbituric acid*). Dissolve about 1 Gm., accurately weighed, in water, acidify with 10 cc. of diluted hydrochloric acid, extract with five successive portions of ether, allow the solvent to evaporate spontaneously, dry the residue to constant weight at 100° C., and weigh: the weight of ethylisopropyl barbituric acid is not less than 78.5 per cent, nor more than 83.0 per cent. Ignite about 1 Gm., accurately weighed, cool, treat the residue with 5 cc. diluted hydrochloric acid, transfer to a 250 cc. beaker, add 25 cc. water and diluted ammonia solution until ammoniacal, warm, add 20 cc. boiling ammonium oxalate T.S., boil and allow to stand overnight; collect the precipitate on an ashless filter paper, wash with dilute

constant weight: the weight of calcium oxide corresponds to not less than 8.0 per cent nor more than 8.5 per cent calcium.

**PROBARBITAL SODIUM.**— $C_9H_{13}N_2NaO_3$ .—M. W. 220.21.—The sodium salt of 5-ethyl-5-isopropyl barbituric acid.

**Caution:** Aqueous solutions of probarbital sodium are not stable but decompose on standing; on boiling, precipitation occurs.

Probarbital sodium is a white hygroscopic powder, soluble in water, slightly soluble in alcohol and practically insoluble in ether and chloroform. An aqueous solution of probarbital sodium has an alkaline reaction to litmus. Dissolve about 0.5 Gm. of probarbital sodium in 100 cc. of water, add an excess of diluted hydrochloric acid, collect the resultant ethylisopropyl barbituric acid on a filter, wash and dry at 100 C.: it melts at 200–205° C. Incinerate about 1 Gm. of probarbital sodium: the residue responds to tests for sodium carbonate. Boil about 0.5 Gm. of probarbital sodium with 5 cc. of 25 per cent sodium hydroxide solution; it is decomposed with evolution of ammonia. Dissolve about 0.3 Gm. of probarbital sodium in 10 cc. of water and divide into two portions. To one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in an excess of strong ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in an excess of strong ammonia solution.

Dissolve about 0.5 Gm. of probarbital sodium in 50 cc. of water, add 5 cc. of diluted nitric acid and filter through paper: separate portions of 10 cc. each of the filtrate yield no opalescence on the addition of 1 cc. of silver nitrate solution (*chloride*); no turbidity on the addition of 1 cc. of barium nitrate T.S. (*sulfate*). To about 0.2 Gm. of probarbital sodium in 25 cc. of water, add 1 cc. of diluted hydrochloric acid and filter through paper: the filtrate yields no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*). Add about 0.1 Gm. of probarbital sodium to 1 cc. of sulfuric acid: the solution is colorless (*readily carbonizable substances*).

Transfer about 1 Gm. of probarbital sodium accurately weighed, to a glass stoppered cylinder, add 50 cc. of anhydrous ether, stopper and shake for ten minutes; decant the supernatant liquid through filter paper and repeat twice, using 25 cc. and 15 cc. portions, respectively, of ether, utilizing the same filter; evaporate the combined filtrates to dryness in a tared beaker and dry to constant weight at 90° C.: the residue does not exceed 0.2 per cent (*uncombined ethylisopropyl barbituric acid*).

Dry about 1 Gm. of probarbital sodium, accurately weighed, to constant weight at 100 C.: the loss does not exceed 2 per cent. Transfer about 0.5 Gm. of probarbital sodium, accurately weighed, to a suitable Squibb separatory funnel, add 50 cc. of water, followed by addition of 10 cc. of diluted hydrochloric acid; extract with eight successive 25 cc. portions of ether, evaporate the combined ether extracts to dryness in a stream of warm air and dry to constant weight at 100° C.: the amount of ethylisopropyl barbituric acid corresponds to not less than 88.5 per cent nor more than 90.5 per cent, calculated to the dried substance. Transfer the acidified aqueous portion from the foregoing extraction to a tared platinum dish and evaporate to dryness on a steam bath; to the residue obtained, add 5 cc. of sulfuric acid; heat *cautiously* until the excess of sulfuric acid has been volatilized; repeat twice, using portions of 1 cc. each of sulfuric acid each time; add about 0.5 Gm. of ammonium carbonate; ignite to constant weight; and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 9.5 per cent nor more than 11.5 per cent when calculated to the dried substance.

**PROPALLYLONAL.**— $C_{10}H_{13}BrN_2O_3$ .—M. W. 289.14.—5-Isopropyl-5- $\beta$ -bromallyl barbituric acid.

Propallylonal occurs as a colorless, crystalline, odorless powder, with a slightly bitter taste. It is readily soluble in alcohol, glacial acetic acid and acetone; and sparingly soluble in ether, chloroform, benzene and

water. A saturated aqueous solution is acid to litmus paper. Propallylonal melts at 177-179° C.

Fuse about 0.1 Gm. of propallylonal and 1 Gm. of crushed potassium hydroxide, previously moistened with 1 cc. of alcohol, in a nickel crucible: it is decomposed with the evolution of ammonia. Cool, dissolve the residue in 10 cc. of water, add 10 cc. of diluted nitric acid and filter through paper. To the filtrate add 5 cc. of silver nitrate T.S.: a curdy, dirty white precipitate results, soluble in a large excess of strong ammonia solution. Place approximately 0.3 Gm. of propallylonal in a 25 cc. glass stoppered cylinder, add a mixture of 1 cc. sodium hydroxide T.S. and 5 cc. of water, shake the contents for one minute, filter through paper and divide into two portions. To one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in 10 cc. of diluted ammonia solution. To the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in 5 cc. of diluted ammonia solution.

Boil about 0.5 Gm. of propallylonal with 50 cc. of water for two minutes: no odor develops. Cool and filter. Separate portions of 10 cc. each of the filtrate yield no opalescence with 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S. (*soluble halides*); no turbidity with 1 cc. of diluted nitric acid and 1 cc. of barium nitrate T.S. (*sulfate*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Ash about 1 Gm. of propallylonal, accurately weighed: the residue does not exceed 0.1 per cent. Dissolve about 0.5 Gm., accurately weighed, in 25 cc. of previously neutralized alcohol, dilute with an equal volume of water and titrate with tenth-normal sodium hydroxide, using thymolphthalein T.S. as an indicator: the amount of tenth-normal sodium hydroxide consumed corresponds to not less than 98.5 per cent, nor more than 101.5 per cent 5-isopropyl-5-( $\beta$ )-bromallyl-barbituric acid. Do a Carius determination on about 0.25 Gm. of propallylonal, accurately weighed: the bromine found should be not less than 27.5 per cent, nor more than 27.9 per cent.

### PROPYL THIOURACIL.— $C_7H_{10}N_2OS$ .—M. W. 170.23. —6-propyl-2-thiouracil.

Propyl thiouracil occurs as a bitter tasting white, powdery, crystalline substance of starch-like appearance to the eye and to the touch. It melts sharply in the range 218-220° C. It is sparingly soluble in alcohol, slightly soluble in chloroform and ether, very slightly soluble in water and practically insoluble in benzene.

Add 1 cc. of strong ammonia solution to 25 mg. of propyl thiouracil: complete solution occurs (*distinction from thiouracil*).

Slowly add bromine water to about 25 mg. of propyl thiouracil in a test tube until complete solution is effected. Discharge the color with heat. Cool and add 10 cc. of saturated barium hydroxide solution: a white precipitate forms (*distinction from thiouracil, which yields a white precipitate that turns purple within a minute*).

Dry 0.5 Gm. of propyl thiouracil, accurately weighed, to constant weight at 100° C.: the loss in weight does not exceed 0.5 per cent.

Char about 0.5 Gm. of propyl thiouracil, accurately weighed; cool, add a few drops of sulfuric acid to the cooled mass and ignite: the amount of residue is not more than 0.1 per cent.

Add 4 cc. of water and 1 cc. of silver nitrate T.S. to 0.5 Gm. of propyl thiouracil in a test tube. Add 5 cc. of nitric acid and allow to stand until the reaction is complete. Expel the oxides of nitrogen by heating, dilute with 10 cc. of water, and cool to room temperature: the turbidity does not exceed that of 0.1 cc. of fiftieth-normal hydrochloric acid used as a control (*halides*).

Heat 25 cc. of water containing 0.5 Gm. of propyl thiouracil for ten minutes on a steam bath. Cool, filter and wash the filter paper; adjust the volume of filtrate to 25 cc. with the washings. Add 1 cc. of barium chloride T.S. and 1 cc. of diluted hydrochloric acid: the turbidity does not exceed that of 0.1 cc. of fiftieth-normal sulfuric acid used as a control (*sulfates*).

Dissolve 1 Gm. of the propyl thiouracil in sufficient sodium hydroxide T.S. to give complete solution, and dilute to 20 cc. with water. Add 5

drops of sodium sulfide T.S.: no more turbidity develops than corresponds to 20 p.p.m. of lead (*U. S. P. XIII*).

Weigh, accurately, about 0.5 Gm. of propyl thiouracil and transfer to a 400 cc. beaker containing 100 cc. of neutralized alcohol. Add 5 drops of phenolphthalein T.S. Slowly titrate with tenth-normal sodium hydroxide, stirring constantly until complete solution is effected. Continue the titration to the first faint pink color. Each cc. of tenth-normal sodium hydroxide solution is equivalent to 0.01702 Gm. of propyl thiouracil: the propyl thiouracil content is not less than 95 per cent nor more than 105 per cent.

**PSYLLIUM HYDROPHYLIC MUCILLOID WITH DEXTROSE.**—A mixture containing about 50 per cent of powdered mucilaginous portion (outer epidermis) of blonde psyllium seeds (*Plantago ovata*-Forsk) and powdered anhydrous dextrose, with sodium bicarbonate 0.2 per cent, monobasic potassium phosphate 0.25 per cent, citric acid 0.33 per cent and benzyl benzoate 0.04 per cent.

Psyllium hydrophyllic muciloid is a white to cream colored, slightly granular powder, possessing little or no odor and a slightly acid taste. A uniform suspension is formed when 10 Gm. of the powder is stirred rapidly into 250 cc. of water. As the hydration and swelling of the mucilaginous portion progresses, the mixture assumes a soft gelatinous consistency.

Place about 10 Gm. of psyllium hydrophyllic muciloid in a dry 25 cc. glass stoppered graduate. Fill the graduate to the 25 cc. mark with a solution made by mixing 73 cc. of chloroform and 27 cc. of carbon tetrachloride. Stopper the graduate and mix the contents thoroughly. Set the graduate aside and observe the contents at the end of two hours: a light colored layer appears at the bottom of the tube, approximately equal in volume to a brownish colored layer which appears at the top of the tube. Mechanically separate the layers formed in the graduate and dry the material at 80° C.: powder from the lower layer is soluble in water and responds to tests for dextrose; powder from the upper layer forms a mucilage with water and is microscopically identical with fragmented material obtained from the outer epidermis of blonde psyllium seed (*Plantago ovata*-Forsk).

Transfer 50 Gm. of Psyllium hydrophyllic muciloid to a suitable flask and determine the moisture content by means of the method for moisture by toluene distillation described in the *U. S. P. XIII*, p. 712: the moisture content found is not more than 4 per cent.

Transfer exactly 20 Gm. of psyllium hydrophyllic muciloid to a 150 cc. beaker, add 0.1 Gm. of decolorizing charcoal and 30 cc. of 80 per cent, V/V, ethyl alcohol preheated to 65-70° C. Stir the mixture thoroughly for three minutes and filter, while still warm, into a 50 cc. volumetric flask. Rinse the beaker twice with 7 to 9 cc. of warm 80 per cent alcohol and filter the rinsings through the residue on the filter paper, adding the washings directly to the volumetric flask. Cool to 25° C., add three drops of strong ammonia solution, fill to the mark with 80 per cent alcohol and mix the contents of the flask. Allow the mixture to stand for ten minutes and then determine the optical rotation of a portion of the solution in a 2 decimeter tube, using sodium light. Multiply the observed angular rotation by 21.7 to obtain the percentage of anhydrous dextrose present in the specimen taken: the amount of dextrose found is not less than 46 per cent nor more than 50 per cent.

**PURIFIED CHONDODENDRON TOMENTOSIUM EXTRACT.**—A curare preparation containing therapeutically desirable constituents of curare.

Dilute in a large Pyrex test tube 0.25 cc. of purified chondodendrum tomentosum extract with 25 cc. of distilled water and add 0.2 cc. of concentrated sulfuric acid and 2 cc. of 1 per cent potassium iodate solu-

tion. Mix and warm in a water bath at 50° C. for one-half hour. A yellow color is developed.

The physiologic activity of purified chondrodendrum tomentosum extract is determined on rabbits: the provisional unit is equivalent to the potency of 0.15 mg. of d-tubocurarine chloride.

**PYRETHRUM OINTMENT.**—Pyrethrum ointment is an unctuous, yellowish green mass.

Place 5 Gm. of pyrethrum ointment in a suitable flask, add 25 cc. of half-normal alcoholic potassium hydroxide solution and an equal volume of water, and heat the mixture under a reflux condenser for five minutes. The alcohol is removed by evaporation, the mixture cooled and allowed to separate. Remove the liquid by decantation, add sufficient barium chloride T.S., thoroughly mix and allow to separate. To the mixture add 1 cc. of sulfuric acid to remove the excess of barium salt. To about 5 cc. of the filtrate add an equal volume of mercuric sulfate T.S.: a pink color develops immediately, becomes deeper on standing and finally changes to green with the development of turbidity or a precipitate (*monocarboxylic acid*).

Determine the pyrethrin content by the procedure (with slight modification) described by Seil in *Soap* in May 1934; the combined pyrethrin content (pyrethrins I and II) is not less than 0.75 per cent nor more than 1 per cent.

**PYRIDOXINE HYDROCHLORIDE.**— $C_8H_{11}O_3N.HCl$ .—M. W. 205.64.—2-Methyl-3-hydroxy-4,5-di-(hydroxymethyl)-pyridine hydrochloride.—Vitamin B<sub>6</sub> hydrochloride.

Pyridoxine hydrochloride occurs as a white, odorless, crystalline powder which melts with decomposition between 200° and 212° C. Under the polarizing microscope it appears as thick, birefringent rods and broken fragments. When recrystallized from methanol containing a few drops of concentrated hydrochloric acid, needle-shaped crystals are obtained which are birefringent and exhibit oblique extinction. In the crystalline state it is reasonably stable to light and air. Acidic aqueous solutions of pyridoxine hydrochloride are stable and may be heated for thirty minutes at 120 C. without decomposition. It is soluble in water (22 Gm. per 100 cc.); slightly soluble in alcohol (1.1 Gm. per 100 cc.); sparingly soluble in acetone; and practically insoluble in ether. Aqueous solutions are acidic (pH about 3.0 for a concentration of 10 mg. per cc.), produce a red color with ferric chloride T.S., yield a precipitate with phosphotungstic acid T.S. and with silver nitrate T.S. which is insoluble in nitric acid but soluble in strong ammonia solution.

Dissolve a few crystals of pyridoxine hydrochloride in 2 cc. of alcohol. Add 2 drops of ammonium hydroxide T.S. and 1 cc. of 2,6-dichloroquinone chloroimide solution (0.01 per cent in alcohol): a deep blue color forms on standing.

Char 0.4 Gm. of pyridoxine hydrochloride. Boil the charred mass with a mixture of 2 cc. of concentrated nitric acid and 8 cc. of water; filter, wash with water, evaporate the filtrate to dryness and dissolve the residue in 0.5 cc. of tenth-normal hydrochloric acid; dilute to 5 cc. with water and add 5 cc. of hydrogen sulfide T.S.: any color produced does not exceed that of a blank control containing 0.02 mg. of lead.

When dried over sulfuric acid, anhydrous calcium sulfate or anhydrous magnesium perchlorate for 24 hours, the loss in weight does not exceed 0.2 per cent.

Determine the carbon and hydrogen content by combustion: the carbon content is not less than 46.5 nor more than 46.9 per cent; the hydrogen content is not less than 5.6 nor more than 6.0 per cent. The residue from the carbon-hydrogen determination, or from an ash determination, does not exceed 0.05 per cent.

Determine the nitrogen content: the amount found is not less than 6.6 nor more than 6.9 per cent.

**TABLETS AND SOLUTIONS OF PYRIDOXINE HYDROCHLORIDE.**

The following reagents are necessary: 1, Barbitol Buffer.—Dissolve 18.0 Gm. sodium diethylbarbiturate in 700 cc. of distilled water and titrate



with normal hydrochloric acid to a  $pH$  of 7.5 to 7.7, using a glass electrode. Filter off the precipitate of diethylbarbituric acid. (If the buffer is allowed to stand over twenty-four hours, the  $pH$  must be readjusted with either normal hydrochloric acid or normal sodium hydroxide to a  $pH$  of 7.5 to 7.7.)

2. Chloroimide Reagent.—Dissolve 25.0 mg. 2,6-dichloroquinone chloroimide in 100 cc. of acid-free butanol. If the reagent is to be kept for some time, it must be stored in a brown, glass-stoppered bottle at refrigerator temperatures; treated thus, it is stable for about two weeks.

3. Standard Solution.—10.0 mg. of dried crystalline pyridoxine hydrochloride is dissolved in exactly 100 cc. of absolute alcohol. If the solution is to be used immediately, 95 per cent alcohol may be employed. (In the absence of a microbalance, a larger quantity may be weighed and appropriate dilutions made from the more concentrated stock solution.)

Procedure.—Dilute the pyridoxine hydrochloride solutions to be tested to a final concentration of 0.10 mg. of pyridoxine hydrochloride per cubic centimeter. In the case of tablets, a sufficient number—ten or more—are transferred to a volumetric flask, water added and the flask shaken to disintegrate the tablets. After diluting to the mark, the solution is filtered, the first 25 cc. discarded and the next 25 cc. saved for the test.

In the following procedures the preparation of the standard and unknown must be carried on concurrently to allow the same amount of time for the development of color in the two solutions:

Transfer 5.0 cc. of the solution to be tested (after diluting as indicated) to a 50 cc. volumetric flask. Add 5.0 cc. of the barbitol buffer and 20 cc. of alcohol.

Prepare a standard solution for comparison by transferring 5.0 cc. of the standard pyridoxine hydrochloride solution to a 50 cc. volumetric flask, adding 5.0 cc. of barbitol buffer, 15 cc. of alcohol and 5 cc. of water.

Now add to both solutions 5.0 cc. of butanol chloroimide reagent, start timing, and shake intermittently for 20 minutes. Dilute to the mark with alcohol and compare in a colorimeter. The pyridoxine hydrochloride found is not less than 93 or more than 107 per cent.

**QUINIDINE.** —  $C_{20}H_{24}N_2O_2 \cdot 2H_2O$ . — M. W. 408.48. — A stereoisomer of quinine obtained along with quinine from the bark of various species of *Cinchona*.

Quinidine occurs in white crystals or as an amorphous, white powder. It is odorless, has an intensely bitter and persistent taste, and effloresces in dry air. It is very slightly soluble in water, soluble in alcohol and ether, freely soluble in chloroform and very slightly soluble in petroleum benzene. The saturated aqueous solution of quinidine is alkaline to litmus and its alcoholic solution is dextrorotatory. A solution of quinidine in diluted sulfuric acid (1 in 1,000) shows a strong blue fluorescence. Quinidine loses its water of hydration at  $100^\circ C$ . The dried alkaloid melts at about  $168^\circ C$ .

Add a few drops of bromine T.S. to 10 cc. of an aqueous solution of quinidine (1 in 1,000), prepared with just sufficient diluted sulfuric acid to produce complete solution, and follow with diluted ammonia solution in slight excess: the liquid acquires an emerald-green color.

Dissolve about 0.1 Gm. of quinidine in 15 cc. of hot water containing a few drops of diluted sulfuric acid, cool the solution, add 1 cc. of silver nitrate T.S. and stir the mixture with a glass rod: a white, crystalline precipitate forms after a short interval (*distinction from many other alkaloids*).

Dissolve about 0.1 Gm. of quinidine in 10 cc. of warm water containing a slight excess of diluted hydrochloric acid; add an excess of potassium iodide T.S. and agitate: an orange yellow, crystalline precipitate forms after an interval (*distinction from quinine*).

Dissolve 0.5 Gm. of quinidine in 15 cc. of boiling distilled water, with just enough sulfuric acid to form a solution neutral to litmus paper, and add 5 cc. of potassium iodide T.S. Agitate the mixture gently, cool it to  $15^\circ C$ , and keep it at this temperature for one hour, with occasional stirring: a white precipitate is formed (*difference from quinine*). Filter out the precipitate and add 2 drops of diluted ammonia solution to the filtrate: not more than a slight turbidity results (*limit of other*

*cinchona alkaloids*). Care must be taken to have the liquid perfectly neutral after the addition of the potassium iodide T.S.; if it is slightly acid, very dilute ammonia water must be added, drop by drop, with constant stirring until exact neutrality to litmus is attained.

A solution of about 0.1 Gm. of quinidine in 5 cc. of sulfuric acid is not darker than pale yellow (*organic impurities*).

Incinerate about 1 Gm. of quinidine, accurately weighed: the ash does not exceed 0.1 per cent.

Dry about 1 Gm. of quinidine, accurately weighed, to constant weight at 100° C.: the loss does not exceed 11 per cent.

**QUININE BISMUTH IODIDE.**—A substance of variable composition containing between 18.0 and 20.1 per cent of bismuth, between 48.7 and 53.5 per cent of iodine; and quinine.

Quinine bismuth iodide is a red powder that clings to most surfaces even when it is dry. It is insoluble in water and most organic solvents.

Treat about 0.5 Gm. of quinine bismuth iodide with 15 cc. of 20 per cent potassium hydroxide solution, warm, add 50 cc. of water, filter off the insoluble material, wash with water, dry at 100° C., extract with five 10 cc. portions of benzene, evaporate the benzene and dry the residue at 100° C.: the residue melts at 171° C. and responds to tests for quinine. Ash the filter and undissolved precipitate in a quartz crucible: a yellow residue remains.

Treat about 0.1 Gm. of quinine bismuth iodide with about 1 cc. of nitric acid: the material blackens. Add 10 cc. of water and boil: violet colored vapors are given off.

Shake 30 mg. of quinine bismuth iodide with 4 cc. of water, filter through a pledget of cotton, add 1 cc. of chloroform and 0.3 cc. each of diluted hydrochloric acid and ferric chloride T.S.; shake and allow to stand five minutes: the chloroform does not acquire a purple tinge (*iodides*).

Shake 0.75 Gm. of quinine bismuth iodide with 4 cc. of potassium iodide T.S., filter, add 1 cc. of chloroform to the filtrate, shake and allow to stand five minutes: the chloroform does not acquire a purple tinge (*iodine*).

Transfer about 0.5 Gm. of quinine bismuth iodide, accurately weighed, to a wide mouth weighing bottle and dry in a vacuum over sulfuric acid to constant weight: it loses not more than 1 per cent in weight. Transfer about 0.5 Gm. of the original, accurately weighed, to a 600 cc. beaker, add nitric acid until the color changes to black, add 100 cc. of water and boil until clear and almost colorless, add an excess of strong ammonia solution and 20 cc. of ammonium carbonate T.S., allow to stand three hours, filter and wash the precipitate with water. Ash the filter paper containing the precipitate in a weighed quartz crucible, add a few drops of nitric acid to the residue, evaporate and ignite to constant weight, cool in a desiccator and weigh: the bismuth oxide weighed is equivalent to not less than 18.0 per cent nor more than 20.1 per cent of bismuth. Transfer about 0.12 Gm. of the original, accurately weighed, to a glass capsule, transfer this capsule to a Carius tube containing 30 cc. of nitric acid and 0.2 Gm. of silver nitrate, seal and heat for seven hours at 210° C.; cool, open the tube, transfer the contents to a large beaker and dilute to 500 cc.; allow to stand for 4 hours, filter through a Gooch crucible, wash with 1 per cent nitric acid, dry at 100° C., cool in a desiccator and weigh: the silver iodide is equivalent to not less than 48.75 per cent nor more than 53.50 per cent iodine.

**RACÉPHEDRINE.**— $C_{10}H_{15}NO$ .—M. W. 165.23.—*d*, *l*-Ephedrine.—*d*, *l*-1-Phenyl-2-methylaminopropanol-1.

Racephedrine is a colorless, crystalline substance. The melting point of the free base is 79° C. (microscope heating stage). It is readily soluble in water, alcohol and ether. Weigh out, accurately, 0.2 Gm. of racephedrine, transfer to a desiccator and dry over phosphorus pentoxide for fifteen hours at room temperature: the loss of moisture is not more than 0.5 per cent. Ignite 0.1 Gm. of racephedrine, accurately weighed, and

previously dried to constant weight: no residue remains. Dissolve approximately 0.5 Gm. of racephedrine in 20 cc. of water: the aqueous solution does not show optical activity and does not give the U. S. P. chloride and sulfate tests.

For further identification tests, see the monograph for racephedrine hydrochloride.

Transfer 0.25 Gm. of racephedrine, accurately weighed, and previously dried over phosphorus pentoxide for five hours at room temperature, to a beaker. Add 10 cc. of distilled water and titrate with tenth-normal sulfuric acid in a slight excess, using methyl red T.S. as indicator. Back titrate with tenth-normal sodium hydroxide. Each cc. of tenth-normal sulfuric acid is equivalent to 0.01651 Gm. of anhydrous racephedrine.

**RACÆPHEDRINE HYDROCHLORIDE.** —  $C_{10}H_{16}Cl$   
NO.—M. W. 201.69.—*d*, *l*-1-Phenyl-2-methylaminopropanol-1.

Racephedrine hydrochloride (synthetic racemic ephedrine hydrochloride) is a colorless, crystalline substance. The melting point of crystalline racephedrine hydrochloride is 187-188° C. (microscope heating stage). The solubility in water is 1 part of substance in 4 parts of water at 20° C.; in alcohol, 1 part of substance in 25 parts of 95 per cent ethyl alcohol. The aqueous solution is neutral to litmus.

Weigh, accurately, 0.2 Gm. of racephedrine hydrochloride and keep over phosphorus pentoxide in an Abderhalden drier at 80° C., exhausted to 2 mm. of mercury for five hours: the loss of moisture is not more than 2 per cent. Ignite 0.2 Gm. of racephedrine hydrochloride, accurately weighed, and previously dried to constant weight, as described: no residue remains. Dissolve approximately 0.5 Gm. in 20 cc. of water: the aqueous solution of racephedrine hydrochloride does not show optical activity. The solution gives the U. S. P. test for chlorides. On addition of diluted ammonia solution or sodium carbonate T.S., no turbidity appears. Slightly acidify 3 cc. of the solution with diluted hydrochloric acid (0.5 cc.): no precipitate occurs on the addition of barium chloride T.S. (0.5 cc.) (*sulfates*).

Dissolve approximately 0.02 Gm. of racephedrine hydrochloride in 1 cc. of concentrated sulfuric acid: no color is formed. To approximately 0.2 Gm. dissolved in 1 cc. of distilled water add 2 cc. of 20 per cent sodium hydroxide solution: oily drops are formed. Extract the milky turbid mixture twice with 25 cc. of ether: the (racephedrine) base crystallizes out on slow evaporation of the ether; after recrystallization from ether and drying at room temperature over phosphorus pentoxide in a slight vacuum, the racephedrine melts at 76° C.

Dissolve approximately 0.2 Gm. of racephedrine in 8 cc. of distilled water; add 1 drop of 2 per cent cupric sulfate solution and 1 cc. of 20 per cent sodium hydroxide solution: a purple color is developed which, on shaking with ether, is partially dissolved in the ether layer. Evaporate the ether layer: a pinkish residue remains. Place a drop of a 5 per cent solution of racephedrine hydrochloride on a microscope slide and introduce a small solid particle of potassium oxalate at an edge of the drop: a crystalline precipitate immediately appears. The form of the crystals allows the distinction between optically active and racemic forms of ephedrine hydrochloride. The former gives bundles of needles and prisms; the latter, thin plates.

Dissolve 0.25 Gm. of racephedrine hydrochloride, accurately weighed, and previously dried over sulfuric acid for 5 hours, in 20 cc. of distilled water, and transfer the solution to a continuous liquid-liquid extractor. Add 3 cc. of 1 normal sodium hydroxide and extract with sufficient peroxide free ether (35 cc.) for 3 to 5 hours. Wash the extract twice with 10 cc. of distilled water and extract the wash water twice with 10 cc. portions of ether. Combine the ether extracts and extract the ether with 15 cc. of tenth-normal sulfuric acid. Wash the combined ether extracts twice with 10 cc. of distilled water. Carefully evaporate to 20 cc. the acidified water solution and back titrate the excess acid with tenth-normal sodium hydroxide: the anhydrous racephedrine is not more than 82.5 per cent nor less than 80.0 per cent of the weight of racephedrine hydrochloride. (One cc. of tenth-normal sulfuric acid is equivalent to 0.01651 Gm. of anhydrous racephedrine.)

**RACÊPHEDRINE SULFATE.**— $C_{10}H_{17}NO_5S$ .—M. W. 263.3.—*d*, *l*-1-Phenyl-2-methylaminopropanol-1.

Racêphedrine sulfate is a colorless, crystalline substance. The melting point is  $247^{\circ}C$ . (microscope heating stage). The solubility is fair in water and alcohol. Dissolve 0.5 Gm. in 25 cc. of distilled water. The aqueous solution is neutral to litmus and does not show optical activity. The U. S. P. test for chloride is also negative. Weigh out accurately 0.25 Gm. of racêphedrine sulfate and dry to constant weight over sulfuric acid in a desiccator at room temperature: the loss is not more than 2 per cent of its weight. Ash 0.25 Gm. of racêphedrine sulfate: the residue should not exceed 0.2 mg. Assay for anhydrous racêphedrine, as described in the monograph for racêphedrine hydrochloride: the racêphedrine content is not less than 75.5 nor more than 77.5 per cent.

**SALICYL SALICYLIC ACID.**— $C_{14}H_{10}O_5$ .—M. W. 129.11.—The salicylic ester of salicylic acid.

Salicyl salicylic acid occurs as a white, odorless, tasteless, stable crystalline powder. It is soluble in alcohol, ether and solutions of alkalis; slightly soluble in benzene; and insoluble in water and dilute acids. Salicyl salicylic acid melts at  $147^{\circ}$  to  $149^{\circ}C$ .

Dissolve 0.5 Gm. of salicyl salicylic acid in 5 cc. of sulfuric acid: no more than a faint yellow color appears (*readily carbonizable substances*). Shake 1 Gm. of salicyl salicylic acid with 25 cc. of cold water, filter and add 1 cc. of ferric chloride T.S.: no violet color appears (*free salicylic acid*). Dissolve 0.5 Gm. of salicyl salicylic acid in 10 cc. of alcohol and add 1 cc. of diluted nitric acid and 1 cc. of silver nitrate T.S.: no precipitate is produced (*chlorides*).

Ignite about 2 Gm. of salicyl salicylic acid, accurately weighed: the ash does not exceed 0.25 per cent. Dry about 1 Gm. of salicyl salicylic acid, accurately weighed, to constant weight at  $100^{\circ}C$ : the loss in weight does not exceed 0.5 per cent.

Transfer about 0.5 Gm. of salicyl salicylic acid, previously dried and accurately weighed, to a 200 cc. flask and add 50 cc. of diluted alcohol which has been previously neutralized to phenolphthalein T.S. Add to this solution 50 cc. of tenth-normal sodium hydroxide and reflux for one hour; cool to room temperature and titrate the excess alkali with tenth-normal hydrochloric acid, using phenolphthalein T.S. as indicator: the salicyl salicylic acid content is not less than 99 per cent. Each cc. of tenth-normal sodium hydroxide is equivalent to 0.01291 Gm. of salicyl salicylic acid.

**SCARLET RED SULFONATE.**— $C_{22}H_{14}N_4Na_2O_7S_2$ .—M. W. 556.49.—The sodium salt of azobenzenedisulfonic acid azobetanaphthol.

Scarlet red sulfonate is a dark, brownish-red, odorless powder. It is soluble in water; slightly soluble in ether, alcohol and acetone; almost insoluble in chloroform, benzene, fixed oils, fats and petroleum.

Add diluted hydrochloric acid to a concentrated, aqueous solution of scarlet red sulfonate: red floccules separate from the orange red solution. Add sodium hydroxide T.S. to a concentrated aqueous solution of the substance: a brownish-red precipitate forms. Treat the substance with concentrated sulfuric acid: a green solution results which becomes blue on the addition of water, and on further dilution, brownish-red floccules separate. Dissolve about 0.1 Gm. of the substance in 5 cc. of glacial acetic acid, heat to boiling, add zinc dust and continue the boiling: the liquid becomes almost colorless.

**SCILLAREN-Sandoz.**—A mixture of the natural glycosides, scillaren-A and scillaren-B, occurring in fresh squill *Urginea maritima*, in the proportions in which they exist in the fresh crude drug; namely, about 2 parts of scillaren-A to

1 part of scillaren-B. Completely dried Scillaren contains approximately 98 per cent of the active glycosides.

Scillaren occurs as a white or yellowish-white, odorless granular powder, possessing a very bitter taste. It is freely soluble in absolute ethyl alcohol, 1 in 5, and in methyl alcohol, 1 in 5; sparingly soluble in water, 1 in 3,000; and practically insoluble in chloroform and in ether. An aqueous solution is neutral toward litmus. An alcoholic solution of Scillaren is levorotatory.

Dissolve about 0.001 Gm. of Scillaren in 0.1 cc. of methyl alcohol, add 3 cc. of acetic anhydride, followed by the addition of 0.1 cc. of sulfuric acid, agitate and cool; a violet-red color results, immediately turning to a bluish green (*this color reaction is due to the mixture of aglucones*). Dissolve about 0.1 Gm. in 10 cc. of methyl alcohol, add 10 cc. of tenth-normal sulfuric acid and heat the mixture under a reflux condenser on a steam bath; after five minutes the aglucone, scillaridin-A, begins to crystallize; continue heating for thirty minutes, cool, collect the resultant aglucone on a filter, wash with water and dry at 105° C. The melting point of the aglucone is not definite, occurring with decomposition at about 220° C. Scillaridin-A responds to the color reaction characteristic for scillaren-A given below. On heating the filtrate for one hour on a steam bath without a reflux condenser, the hydrolysis progresses with a partial resinification of the mixed aglucones; they separate partially in the form of yellowish-brown oily droplets which, on cooling, solidify into a brownish brittle mass. Neutralize the solution with tenth-normal sodium hydroxide; remove the separated residue consists of a mixture of the two aglucones, namely, scillaridin A and B, by filtration; the filtrate contains nonhydrolyzable scillaren-B and cleaved sugar but is entirely free from scillaren-A. Boil about 2 cc. of the filtrate with 5 cc. of alkaline cupric tartrate T.S.: a precipitate of copper results. Transfer the remainder of the filtrate to a glass stoppered Erlenmeyer flask, add 25 cc. of ethyl acetate, and 15 Gm. of a finely powdered ammonium sulfate; decant the ethyl acetate and the aqueous ammonium sulfate layers into a suitable Squibb separatory funnel, shake vigorously and allow the two layers to separate completely; filter the ethyl acetate solution through paper by the aid of suction into a small flask and evaporate to dryness. The residue mixed with 20 cc. of acetic anhydride and 0.5 cc. of sulfuric acid gives a violet-blue color, changing to the blue characteristic of scillaren-B.

Dissolve about 0.025 Gm. of Scillaren in 2 cc. of methyl alcohol: a clear colorless solution results, which remains clear on dilution with an equal volume of carbon dioxide-free water (*aglucone*). Add to the foregoing solution 1 cc. of a mixture of equal volumes of methyl alcohol and lead acetate T.S.: a slight yellow coloration and opalescence results in ten minutes, but no precipitate (*appreciable amounts of tannoid substances*). Dissolve about 0.025 Gm. in a mixture of 2 cc. of methyl alcohol and 2 cc. of water, add 0.5 cc. of alkaline cupric tartrate T.S. and heat for ten seconds: no turbidity results (*free reducing sugars*).

Dissolve about 0.5 Gm. of Scillaren, accurately weighed, in 25 cc. of 75 per cent (by weight) ethyl alcohol; observe the angular rotation at 20° C.: the specific rotary power in alcohol  $[\alpha]_{20/D}$  falls between -25 and -35.

Ignite about 0.1 Gm. of Scillaren, accurately weighed: the residue does not exceed 0.25 per cent. Dry about 0.2 Gm., accurately weighed, over sulfuric acid in a partially exhausted desiccator for 48 hours at 20° C.: the loss in weight does not exceed 4 per cent. Scillaren dried in a high vacuum at 78° C. for 15 hours loses not more than 6 per cent of its weight.

Weigh out accurately about 0.2 Gm. of Scillaren, previously dried over sulfuric acid in a partial vacuum. Transfer the sample to a 250 cc. Erlenmeyer flask, dissolve it in 5 cc. of water and add 20 cc. of 5 per cent sulfuric acid; heat on a steam bath for six hours; cool and collect the separated crystalline and oily resinous mixture on a Gooch crucible, and wash free from acid with water; dry for 24 hours at 60° C., and weigh: the amount of aglucone found is not less than 48 per cent nor more than 53 per cent.

Scillaren-A, a component of Scillaren, responds to the following tests for identity and purity:

Scillaren-A occurs as small, colorless, odorless crystals or crystalline powder, with a very bitter taste. It is soluble in ethyl alcohol, 1 in 350, in methyl alcohol, 1 in 80; in a mixture of 4 parts by volume of ethyl alcohol and 1 part by volume of water, 1 in 40; and practically insoluble in chloroform and ether. It dissolves in water with difficulty, possessing a neutral reaction toward litmus. The specific rotation in 75 per cent alcohol  $[\alpha]_{20/D}$  falls between  $-72$  and  $-78$  determined on the undried material.

Dissolve about 0.001 Gm. of scillaren-A in 0.1 cc. of methyl alcohol, and add 3 cc. of acetic anhydride and 0.1 cc. of sulfuric acid; shake; a red color results, disappears rapidly and changes to a persistent light green (*this color reaction is due to the aglucone, scillaridin A*). Dissolve about 0.1 Gm. in 10 cc. of methyl alcohol, add 10 cc. of tenth-normal sulfuric acid, heat the mixture under a reflux condenser on a steam bath for thirty minutes, collect the resultant aglucone on a filter paper, wash with water and dry at  $105^{\circ}\text{C}$ .: its melting point is not definite, occurring at about  $220^{\circ}\text{C}$ . The material responds to the foregoing color reaction. The neutralized filtrate reduces alkaline cupric tartrate T.S. immediately.

Dissolve about 0.025 Gm. scillarin-A in 2 cc. of a mixture of 4 parts of ethyl alcohol (by volume) and 1 part of carbon dioxide-free water: a clear colorless solution results, which remains clear on dilution with an equal volume of carbon dioxide-free water (*aglucone*). Add to the foregoing solution 0.1 cc. of lead acetate T.S.: no immediate coloration or precipitate results (*appreciable amounts of tannoid substances*). Dissolve about 0.025 Gm. in a mixture of 2 cc. of methyl alcohol and 2 cc. of water, add 0.5 cc. of alkaline cupric tartrate T.S. and heat to boiling: the blue color persists for some time (*free reducing sugars*). Dissolve about 0.5 Gm. of scillaren-A, accurately weighed, in 25 cc. of 75 per cent (by weight) of ethyl alcohol; observe the angular rotation at  $20^{\circ}\text{C}$ .: the specific rotatory power in alcohol  $[\alpha]_{20/D}$  falls between  $-72$  and  $-78$ .

Ash about 0.1 Gm. of scillaren-A, accurately weighed: the residue does not exceed 0.1 per cent. Dry about 0.2 Gm., accurately weighed, over sulfuric acid in a partially exhausted desiccator for 48 hours at  $20^{\circ}\text{C}$ .: the loss in weight does not exceed 2.5 per cent.

Weigh out accurately about 0.2 Gm. of scillaren-A, previously dried over sulfuric acid in a partial vacuum. Transfer the sample to a 250 cc. Erlenmeyer flask, add 10 cc. of methyl alcohol and 10 cc. of tenth-normal sulfuric acid, reflux on a steam bath for 15 minutes, disconnect the condenser and boil on a steam bath until reduced to about a 10 cc. volume, cool and collect the crystals formed on a Gooch crucible, wash free from acid with water and dry to constant weight at  $105^{\circ}\text{C}$ .: the amount of aglucone found should not be less than 48 per cent, nor more than 53 per cent.

**SCILLAREN-B-Sandoz.**—The amorphous component of the natural mixture of the glycosides occurring in squill, *Urginea maritima*. Completely dried Scillaren-B contains approximately 99.5 per cent active glycosidal substance.

Scillaren-B occurs as a fine white or slightly yellowish-white, odorless, granular powder, possessing a very bitter taste. It is freely soluble in water, and in ethyl and methyl alcohols (1 in 5), very slightly soluble in chloroform (1 in 10,000), and practically insoluble in ether. An aqueous solution is neutral toward litmus. An alcoholic solution of Scillaren-B is dextrorotatory.

Dissolve about 0.001 Gm. of Scillaren-B in 0.1 cc. of methyl alcohol; add 3 cc. of acetic anhydride and followed by the addition of 0.1 cc. of sulfuric acid, agitate and cool: a violet-blue color results, gradually changing to a blue (*this color reaction is presumed to be due to the aglucone, scillaridin-B*). Dissolve about 0.1 Gm. in 10 cc. of methyl alcohol, add 10 cc. of tenth-normal sulfuric acid and heat the mixture under a reflux condenser on a steam bath for 30 minutes: only a slight turbidity results; disconnect the reflux condenser and continue

heating for one hour to remove the methyl alcohol: the aglucone separates as small yellowish-brown greasy lumps which solidify on cooling. Collect the resultant aglucone on a filter paper, wash with water and dry in a partially exhausted desiccator over sulfuric acid: it responds to the foregoing color reaction. The neutralized filtrate reduces alkaline cupric tartrate T.S.

Dissolve about 0.025 Gm. of Scillaren-B in 1 cc. of carbon dioxide free water: a clear and colorless solution results (*aglucone*). Add to the foregoing solution 1 cc. of methyl alcohol, followed by the addition of 1 cc. of lead acetate T.S.: no immediate coloration or precipitate results (*appreciable amounts of tannoid substances*). Dissolve about 0.0025 Gm. in a mixture of 2 cc. methyl alcohol and 2 cc. of water, add 0.5 cc. of alkaline cupric tartrate T.S. and heat for ten seconds: no turbidity results (*reducing free sugars*).

Dissolve about 0.5 Gm. of Scillaren-B, accurately weighed, in 25 cc. of 75 per cent (by weight) of ethyl alcohol; observe the angular rotation at 20° C.: the specific rotatory power in alcohol  $[\alpha]_{20}^D$  falls between + 35 and + 41.

Ignite about 0.1 Gm. of Scillaren-B, accurately weighed: the residue does not exceed 0.1 per cent. Dry about 0.2 Gm., accurately weighed, over sulfuric acid in a partially exhausted desiccator for 48 hours at 20° C.: the loss in weight does not exceed 2 per cent. Scillaren-B dried in a high vacuum at 78° C. for 15 hours loses not more than 5 per cent of its weight.

Weigh out accurately about 0.2 Gm. of Scillaren-B, previously dried over sulfuric acid in a partial vacuum. Transfer the sample to a 250 cc. Erlenmeyer flask, dissolve it in 5 cc. of water and add 20 cc. of a 5 per cent sulfuric acid; heat on a steam bath for six hours, cool, and collect the separated yellowish-brown lumps on a Gooch crucible; wash the precipitate free from acid with water, dry for 24 hours at 60° C., and weigh: the amount of aglucone found is not less than 50 per cent nor more than 57.5 per cent.

**SCOPOLAMINE STABLE-Hoffmann-LaRoche.**—An aqueous solution of pure scopolamine hydrobromide ( $C_{17}H_{22}BrNO_4$ .—M. W. 384.27) protected against decomposition by the addition of 10 per cent of mannite.

Scopolamine Stable-Roche is prepared by dissolving in an aqueous 10 per cent solution of mannite freshly manufactured scopolamine hydrobromide having an optical activity of  $[\alpha]_{15}^D = -26.0^\circ$  (determined in

an aqueous solution containing the equivalent of 4.5 Gm. of anhydrous scopolamine hydrobromide in 100 cc. at a temperature of 15° C. in a 10 decimeter tube). The melting point of scopolamine hydrobromide is 195° C.

The absence of decomposition products is demonstrated by comparing the action of Scopolamine Stable-Roche with that of a freshly prepared solution of Scopolamine hydrobromide by Langer's frog method. In this method the frog heart is stopped by muscarine, or, better, by pilocarpine, and the beat is reestablished by the addition of scopolamine, which is antagonistic to both muscarine and pilocarpine.

**SECONAL SODIUM-Lilly.**— $C_{12}H_{17}N_2NaO_3$ .—M. W. 260.27.—The monosodium salt of 5-allyl-5-(1-methylbutyl) barbituric acid.

Seconal Sodium occurs as a white, hygroscopic, odorless powder, possessing a bitter taste. It is very soluble in water, soluble in alcohol and practically insoluble in ether. An aqueous solution of Seconal Sodium is alkaline to litmus.

Dissolve about 1 Gm. of Seconal Sodium in 100 cc. of distilled water in a 500 cc. beaker and add sufficient 1 per cent acetic acid to make the solution distinctly acid to litmus. Stir vigorously for a few minutes

and add an additional 150 cc. of distilled water. Heat to boiling and boil until the precipitate dissolves and no oily particles float on the surface of the liquid. Allow the solution to stand overnight at room temperature. Collect the resultant crystals of allyl-(1-methylbutyl) barbituric acid on a porous plate and dry at room temperature: the crystals melt between 96° and 100° C. Dissolve 0.3 Gm. of Seconal Sodium in 10 cc. of distilled water and divide the solution into two portions; to one portion add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in excess of diluted ammonia solution; to the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in excess of diluted ammonia solution. Transfer about 0.5 Gm. of Seconal Sodium to a 50 cc. beaker and boil with 5 cc. of a 25 per cent solution of sodium hydroxide: the product decomposes and ammonia is evolved. Dissolve about 0.5 Gm. of Seconal Sodium in 50 cc. of distilled water, add 5 cc. of diluted nitric acid and filter through paper. Separate 10 cc. portions of the filtrate yield no turbidity on the addition of 1 cc. of barium chloride T.S. (*sulfate*) and no more opalescence on the addition of 1 cc. of silver nitrate T.S. than is produced by 0.5 cc. of fiftieth-normal hydrochloric acid in 50 cc. of distilled water (*chloride*). To about 0.2 Gm. of Seconal Sodium add 25 cc. of water and 1 cc. of diluted hydrochloric acid and filter through paper: the filtrate yields no color or precipitate when saturated with hydrogen sulfide (*heavy metals*). A solution prepared by dissolving 0.5 Gm. of Seconal Sodium in 5 cc. of sulfuric acid develops no more color after five minutes standing than matching fluid H described in the U. S. P. XIII, p. 681. Dissolve about 1 Gm. of Seconal Sodium in 10 cc. of water and add one drop of a 5 per cent solution of potassium permanganate: the purple color is discharged and a brown precipitate is formed. Dry about 1 Gm. of Seconal Sodium, accurately weighed, to constant weight at 90° C.: the loss in weight does not exceed 1 per cent.

Transfer about 1 Gm., accurately weighed, of Seconal Sodium to a 250 cc. separatory funnel, add 50 cc. of distilled water and 10 cc. of diluted hydrochloric acid, and extract the mixture with eight successive 25 cc. portions of ether. Filter the ether extracts, evaporate to dryness on the steam bath and dry to constant weight at 90° C.: the allyl-(1-methylbutyl)barbituric acid obtained is not less than 90.5 nor more than 92 per cent, calculated to the dried substance. Evaporate the aqueous residue to dryness on a steam bath, transfer to a tared platinum dish with a minimum of water and add 5 cc. sulfuric acid; cautiously evaporate the excess acid and ignite to constant weight at 900° C.: the weight of sodium sulfate is equivalent to a sodium content of not more than 9.4 nor less than 8.7 per cent, calculated to the dried substance.

Transfer an accurately weighed sample of about 10 mg. to a micro Kjeldahl flask and digest with 2 cc. of sulfuric acid and 0.01 Gm. of selenium. Dilute the clear solution to 10 cc., make alkaline with 30 per cent sodium hydroxide, and distil the ammonia into 10 cc. of one hundredth normal acid, using methyl red T.S. as indicator: the nitrogen content is not more than 10.85 nor less than 10.70 per cent, calculated to the dried substance.

**SHARK LIVER OIL.**—The oil extracted from the livers of the shark, mainly of the variety *Hypoprion brevirostris* (lemon), but any or all of the following varieties may be included: *Odontaspis littoralis* (sand), *Isurus punctatus* (mackerel), *Triakis semifasciatus* (leopard), *Sphyrna zygaena* (hammerhead), *Carcharias obscurus* (dusky), *Ginglymostoma cirratum* (nurse), *Carcharias milberti* (white) and *Carcharias limbatus* (black tip). It is biologically assayed and has a potency of not less than 16,500 units of vitamin A (U. S. P.) per gram and of not less than 40 units of vitamin D (U. S. P.) per gram.

Shark liver oil is an amber to brown oily liquid possessing a fishy odor and taste. It is insoluble in water, slightly soluble in alcohol and soluble in chloroform, ether, benzene, ethyl acetate and carbon



disulfide. The specific gravity is from 0.917 to 0.923 at 25° C. The refractive index is from 1.475 to 1.480 at 20° C.

A solution of one drop of the oil in 1 cc. of chloroform, when shaken with one drop of sulfuric acid, acquires a light violet color, changing to purple and finally brown or blue. Transfer 5 cc. of oil to a centrifuge tube and add 5 cc of benzene; centrifuge for 25 minutes at 25° C.: no precipitate forms and a clear solution remains.

Fill a tall, cylindric, standard oil-sample bottle of about 120 cc. capacity with shark liver oil and immerse in a water bath at about 10° C.: the oil becomes turbid at about 15° C., but it becomes fluid and clear when the bath is then warmed to 45° C.

Transfer 2 Gm. of sharp liver oil, accurately weighed, to an Erlenmeyer flask and dissolve in 20 cc. of a mixture of equal volumes of alcohol and ether, which previously has been neutralized with tenth-normal sodium hydroxide, using five drops of phenolphthalein T. S. as indicator, and titrate with tenth-normal sodium hydroxide to the production of a pink color which persists for fifteen seconds; not more than 1 cc. of tenth-normal sodium hydroxide is required (*free acid*). The amount of unsaponifiable matter as determined by the method of the *U. S. P. XIII*, p. 648, is not less than 3.0 per cent nor more than 6.0 per cent. The saponification value as determined by the method of the *U. S. P. XIII*, p. 647, is not less than 170 nor more than 187. The iodine value as determined by the method of the *U. S. P. XIII*, p. 647, on from 0.18 to 0.20 Gm. of sample, accurately weighed, is not less than 125 nor more than 145.

### SILVER PICRATE.— $C_6H_2AgN_3O_7 \cdot H_2O$ .—M. W. 354.0.

Silver picrate occurs as yellow crystals, slowly discoloring in sunlight. It is sparingly soluble in water and alcohol, slightly soluble in acetone and glycerin, and very slightly soluble in chloroform and ether.

Dissolve about 0.1 Gm. of silver picrate in 10 cc. of water, add 1 cc. nitric acid followed by the addition of 5 cc. of diluted hydrochloric acid, shake thoroughly, filter through paper: the precipitate is soluble in an excess of diluted ammonia solution while the filtrate turns red on the addition of diluted ammonia solution and ammonium sulfide.

Dissolve an accurately weighed quantity of the material in about 150 parts of water, collect the insoluble residue on an ashless filter paper, wash with about 300 cc. of water and ignite: the weight of ash does not exceed 0.5 per cent. To the foregoing filtrate, add 2 cc. of nitric acid and then 5 cc. of diluted hydrochloric acid added a little at a time with constant stirring. Boil, cool, collect the precipitate of silver chloride on a Gooch crucible, wash with diluted nitric acid and water, followed by a small quantity of alcohol and ether; finally dry to constant weight at 120° C.: the amount of silver calculated from the silver chloride found corresponds to not less than 30 per cent, nor more than 32 per cent.

*Caution*—Silver picrate is explosive under certain conditions.

**SOBISMINOL MASS.**—A complex organic bismuth product the chemical nature of which has not been fully established. It is obtained by the interaction of sodium bismuthate, triisopropanolamine and propylene glycol. It contains between 19.25 and 20.25 per cent of bismuth; 0.75 Gm. of sobisminol mass represents 150 mg. of bismuth.

Sobisminol mass occurs as a red-brown to chocolate-brown colored pasty mass, possessing an odor similar to triisopropanolamine and a bitter taste, with a sweetish, metallic after-taste. It is soluble in water and alcohol and partially soluble in ether and acetone. The *pH* of a solution made by dissolving 1 Gm. sobisminol mass in sufficient distilled water to make a volume of 10 cc. should not be above 11.9 as determined with a glass electrode.

Dissolve 1 Gm. of sobisminol mass in 10 cc. of water and halve the solution; to one portion add 5 cc. of 0.5 per cent sodium bicarbonate solution; to the other portion add 5 cc. of 0.1 per cent hydrochloric acid: neither solution yields a precipitate within 15 minutes.

Dissolve 2 Gm. of sobisminol mass in 100 cc. of water; boil a 5 cc. portion: the solution remains clear and unchanged. To a separate portion of 1 cc. add 10 cc. of water and 1 cc. of 5 per cent sodium iodide solution: the solution remains clear. To another 1 cc. portion add 1 cc. of diluted hydrochloric acid, 5 cc. of water and 5 cc. of hydrogen sulfide T.S.: a black precipitate forms. To another 1 cc. portion add 3 cc. of diluted sulfuric acid and 1 cc. of a 5 per cent sodium iodide solution: a red precipitate forms. To a 20 cc. portion add 2 cc. of nitric acid, adding more nitric acid dropwise, if necessary, until the solution is clear; divide into two equal parts; retain one part as a control and add 2 cc. of silver nitrate T.S. to the other part: when compared with the control, not more than a trace of turbidity is apparent (*chloride*). To another 20 cc. portion add 2 cc. of hydrochloric acid, adding more hydrochloric acid dropwise, if necessary, until the solution is clear; divide into two equal parts; retain one part as a control and add 2 cc. of barium chloride T.S. to the other part: when compared with the control, not more than a trace of turbidity is apparent (*sulfate*).

Transfer about 5.0 Gm. of sobisminol mass, accurately weighed, to a 100 cc. volumetric flask, add water to the mark and shake the contents thoroughly. Determine the nitrogen content of an accurately measured 10 cc. portion according to the method described in *Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, p. 27, paragraph 25. In the procedure add 0.1 Gm. of anhydrous copper sulfate and continue the digestion for a period of two and one-half hours after the solution becomes clear: The amount of nitrogen is not less than 3.60 per cent no more than 4.40 per cent.

Dissolve about 0.6 Gm. of sobisminol mass, accurately weighed, in 100 cc. of water and rapidly add 8 cc. of concentrated nitric acid. Add two drops of methyl red T.S. and then add diluted ammonia solution until the solution just turns yellow; add 3 cc. of nitric acid, heat to boiling and slowly add, with cautious stirring, 50 cc. of 10 per cent diammonium phosphate solution; dilute to a volume of about 400 cc. with boiling water and allow the mixture to stand for one hour at 80 C. Collect the precipitate on a tared Gooch crucible by filtering the supernatant liquid, washing the precipitate by decantation with four 50 cc. portions of hot water, passing these washings through the crucible, and finally completing the transfer of the precipitate by means of cold water; dry the crucible and contents at 110° C. for one hour, suspend the crucible within another crucible and ignite gently for 45 minutes, adjusting the flame so that the bottom of the lower crucible is heated to dull redness; cool the crucible and contents and weigh the ignited material as bismuth phosphate; use the factor 0.6875 for the conversion of bismuth phosphate to bismuth: the amount of bismuth found corresponds to not less than 19.25 per cent nor more than 20.25 per cent.

PROPYLENE GLYCOL ( $C_3H_8O_2$ .—M. W. 76.09): The propylene glycol used in the preparation of sobisminol mass and sobisminol solution conforms to The National Formulary standards for this substance, which see.

SODIUM BISMUTHATE ( $NaBiO_3$ .—M. W. 280): The sodium bismuthate used in the preparation of sobisminol mass and sobisminol solution conforms to the following tests for identity and purity:

Sodium bismuthate occurs as a nearly odorless, yellow-brown powder containing not less than 80 per cent of  $NaBiO_3$ .

Dissolve 1 Gm. of sodium bismuthate in a mixture of 5 cc. of hydrochloric acid and 15 cc. of water: a slightly turbid, yellow solution results. Agitate 2 Gm. of sodium bismuthate with 50 cc. of water frequently during one hour: the resultant suspension is alkaline to phenolphthalein; filter, rejecting the first few cubic centimeters: evaporate 25 cc. of the clear filtrate in a tared dish, dry the residue at 120° C. and weigh: the weight of the residue is not more than 0.003 Gm.

Boil 2.5 Gm. of sodium bismuthate and 40 cc. of water for ten minutes, cool, dilute to 50 cc. with water, mix well, filter and divide into 10 cc. portions. To one portion add 0.5 cc. of nitric acid and 1 cc. of silver nitrate T.S.: the turbidity should not be greater than that produced in a control containing 0.025 mg. of chloride ion (*chloride*). To another portion add 0.5 cc. of normal hydrochloric acid, filter, if necessary, and add to the clear filtrate 1 cc. of barium chloride T.S.: the turbidity should not be greater than that produced in a control containing 0.05 mg. of sulfate ion (*sulfate*).

Heat 0.5 Gm. of sodium bismuthate with 3 cc. of sulfuric acid until fumes of sulfur trioxide appear, then complete the test for arsenic according to the method described in the *U. S. P. XIII*, p. 618: the arsenic content should not exceed 2 parts per million.

Dissolve about 0.25 Gm. of sodium bismuthate, accurately weighed, in 8 cc. of nitric acid, dilute with 100 cc. of water, and continue the assay for bismuth as directed in the last paragraph under sobisminol mass; the amount of bismuth found corresponds to not less than 66.5 per cent nor more than 72.5 per cent.

Transfer about 0.7 Gm. of sodium bismuthate, accurately weighed, to a flask and add 25 cc. of ferrous sulfate T.S., stopper the flask, allow it to stand one-half hour with frequent shaking, and titrate the excess ferrous sulfate with tenth-normal potassium permanganate solution: the sodium bismuthate should not be less than 80 per cent  $\text{NaBiO}_3$ . (The ferrous sulfate T.S. must be freshly prepared and standardized by a control titration).

**TRIISOPROPANOLAMINE** ( $\text{C}_9\text{H}_{21}\text{NO}_3$ .—M. W. 191.27): The triisopropanolamine,  $\text{N}(\text{C}_3\text{H}_7\text{OH})_3$ , used in the preparation of sobisminol mass and sobisminol solution responds to the following tests for identity and purity:

Triisopropanolamine occurs as a colorless to pale yellow colored, pasty semicrystalline mass, possessing a slight characteristic odor and a bitter taste. It melts to a clear liquid at a temperature of not less than 46 C. Triisopropanolamine is readily soluble in acetone, alcohol, ether, chloroform and water.

Dissolve 1 Gm. of triisopropanolamine in 10 cc. of water: the solution is alkaline to litmus and only very slightly turbid. Dissolve 1 Gm. of triisopropanolamine in 20 cc. of water and divide the solution into two portions. To one portion add 0.5 cc. normal hydrochloric acid, filter, if necessary, and add to the clear filtrate 1 cc. of barium chloride T.S.: not more than a faint turbidity develops in five minutes (*sulfate*). To the other portion add 0.5 cc. of nitric acid and 1 cc. of silver nitrate T.S.: not more than a faint turbidity is produced (*chloride*).

The arsenic content of triisopropanolamine is not more than 2 p.p.m.; heavy metals are absent (*U. S. P. XIII*, p. 657). Ignite 5 Gm. of triisopropanolamine: the weight of the ash does not exceed 0.05 per cent.

Transfer about 5 Gm. of triisopropanolamine to a 100 cc. volumetric flask and assay for nitrogen as directed under sobisminol mass: the amount of nitrogen found is not less than 7.1 per cent nor more than 7.6 per cent. Dissolve about 1 Gm. triisopropanolamine, accurately weighed, in 50 cc. of distilled water and titrate with half-normal hydrochloric acid, each cc. of which is equivalent to 0.0955 Gm. of triisopropanolamine, using methyl red T.S. as the indicator: the triisopropanolamine content should be not less than 98.5 per cent nor more than 101.5 per cent.

**SOBISMINOL SOLUTION.**—A solution containing a complex organic bismuth product the chemical nature of which has not been fully established. It is obtained by dissolving the products of the interaction of sodium bismuthate, triisopropanolamine and propylene glycol in a mixture of propylene glycol and water. Each cc. of the solution contains between 19.5 and 20.5 mg. of bismuth and 0.5 cc. of propylene glycol.

Sobisminol solution occurs as a clear, dark brown-red colored liquid, possessing an odor similar to triisopropanolamine and a sweet, mildly metallic taste. It is miscible with an equal volume of water or alcohol.

The pH of a portion of sobisminol solution is not below 11.1 nor above 11.5 as determined by means of a glass electrode. The specific gravity of sobisminol solution is not less than 1.064 nor more than 1.066 at 25° C.

Undiluted sobisminol solution responds to the tests for identity and purity stated under sobisminol mass.

Transfer 5 cc. of sobisminol solution, accurately measured, to a 500 cc. beaker and determine the bismuth content according to the

method stated under sobisminol mass: the amount of bismuth found is not less than 0.0195 Gm. nor more than 0.0205 Gm. per cubic centimeter.

Transfer 5 cc. of sobisminol solution, accurately measured, to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the method stated under sobisminol mass: the amount of nitrogen found is not less than 0.0054 Gm. nor more than 0.0060 Gm. per cubic centimeter.

The propylene glycol, sodium bismuthate and triisopropanolamine used in the preparation of sobisminol solution corresponds to the standards for these substances as indicated under sobisminol mass.

### SODIUM DEHYDROCHOLATE.— $C_{24}H_{33}NaO_5$ .—M. W. 424.5.

Sodium Dehydrocholate occurs as a fine, colorless, crystalline powder with a very bitter taste, soluble in water and alcohol. An aqueous solution is alkaline to litmus.

Dissolve about 1 Gm. of sodium dehydrocholate in 200 cc. of water; add an excess of hydrochloric acid; collect the resultant dehydrocholic acid on a filter, wash, and recrystallize from 80 per cent acetic acid; it melts at 233-238° C.

Dissolve about 0.5 Gm. of sodium dehydrocholate in 100 cc. of water, acidify with hydrochloric acid and filter: Separate portions of 10 cc. each of the filtrate yield no turbidity with 1 cc. of barium chloride T.S. (sulfate); no color or precipitate on saturation with hydrogen sulfide (salts of heavy metals).

Dry about 1 Gm. of sodium dehydrocholate accurately weighed, to constant weight at 100 C.: The loss in weight does not exceed 7 per cent. Weigh accurately about 1 Gm. in a tared platinum crucible, add 2 cc. of sulfuric acid, gently heat while fumes of sulfur trioxide are evolved, repeat, using two 1 cc. portions of sulfuric acid, ignite, cool and weigh as sodium sulfate: the percentage of sodium corresponds to not less than 5.3 per cent, nor more than 5.6 per cent, when calculated to the dried substance.

### SODIUM HYPOCHLORITE SOLUTION.—A solution of chlorinated soda, each 100 Gm. of which is stated to contain sodium hypochlorite 4.05 Gm., sodium chloride 2.50 Gm., calcium hydroxide 0.14 Gm., inert salts 0.65 Gm. It contains not less than 3.85 per cent of available chlorine.

Sodium hypochlorite solution is prepared by decomposing chlorinated lime suspended in water with sodium carbonate.

Sodium hypochlorite solution has the properties of Solution of Chlorinated Soda-U. S. P. X. but contains no carbonate. When exposed to air, a pellicle forms on its surface owing to the formation of calcium carbonate.

To about 5 Gm. of sodium hypochlorite solution, accurately weighed, add 50 cc. of distilled water. To the resulting solution, slowly add 10 cc. of a 3 per cent hydrogen peroxide solution, previously rendered neutral. After the reaction is completed, as indicated by the cessation of the evolution of the oxygen, 4 drops of methyl orange T.S. and an excess (measured) of tenth-normal hydrochloric acid are added. Titrate the residual acidity with tenth-normal sodium hydroxide: the alkalinity found corresponds to not more than 0.14 Gm. of calcium hydroxide per 100 Gm. of sodium hypochlorite solution.

Mix in a flask about 5 cc. of sodium hypochlorite solution, accurately weighed, with 50 cc. of distilled water; add 1 Gm. of potassium iodide and 5 cc. of acetic acid and titrate with tenth-normal sodium thiosulfate, starch test solution being used as indicator: it shows not less than 3.85 per cent of available chlorine. Each cc. of tenth-normal sodium thiosulfate used corresponds to 0.003546 Gm. of available chlorine. Due allowance should be made for a decrease in available chlorine content of about 12 per cent per year, calculated from the date of bottling stamped on each bottle.

**SODIUM IODOMETHAMATE.**— $C_8H_3I_2NNa_2O$ .—M. W. 428.95.—Disodium *N*-methyl-3,5-diiodo-4-pyridone-2,6-dicarboxylate.

Sodium iodomethamate occurs as a white, crystalline, odorless powder; very soluble in water; insoluble in acetone, benzene, chloroform, ether and purified petroleum benzene. An aqueous solution is neutral to litmus.

Dissolve about 0.5 Gm. of sodium iodomethamate in 100 cc. of water, add an excess of diluted hydrochloric acid; collect the liberated *N*-methyl-3,5-diiodo-4-pyridoxyl-2,6-dicarboxylic acid on a filter, wash and dry in a desiccator over sulfuric acid under a partial vacuum: it melts at about 174 C., with decomposition: heat the remainder of the resultant acid at its decomposition temperature (about 175 to 180 C.) until no further evolution of gas is noted: the residual substance, *N*-methyl-3,5-diiodo-4-pyridone, thrice recrystallized from water, melts at 214° C.; to 1 cc. of the foregoing filtrate add 10 cc. of cobalt uranyl acetate T.S.: a yellow precipitate results. Dissolve about 0.5 Gm. of sodium iodomethamate in 50 cc. of water, add an excess of hydrochloric acid, filter through paper and divide into two portions. To one portion add 1 cc. of chloroform and 0.1 cc. of ferric chloride solution: no color is imparted to the chloroform layer (*absence of free inorganic iodide*). Saturate the other portion with hydrogen sulfide: no color or precipitate results (*salts of heavy metals*).

Dry about 1 Gm. of sodium iodomethamate, accurately weighed, to constant weight at 100° C.: the loss in weight does not exceed 2 per cent. Transfer about 1 Gm. of sodium iodomethamate, accurately weighed, to a 500 cc. Kjeldahl flask, and determine the nitrogen content according to the official method described in *Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, p. 27, paragraph 25: the percentage of nitrogen corresponds to not less than 2.7 per cent, nor more than 2.9 per cent when calculated to the dried substance. Weigh accurately about 0.5 Gm. of sodium iodomethamate in a tared platinum dish, add 10 cc. of sulfuric acid, gently heat while fumes of iodine and sulfur trioxide are evolved, repeat, using two portions of sulfuric acid; and ignite, cool and weigh as sodium sulfate: the sodium found corresponds to not less than 9.2 per cent nor more than 9.4 per cent when calculated to the dried substance. Transfer about 0.2 Gm. of sodium iodomethamate to a Parr sulfur bomb; determine the iodine content by the Lemp and Broderson Method (*J. Am. Chem. Soc.* 39:2069): the amount of iodine found corresponds to not less than 51 per cent nor more than 53 per cent when calculated to the dried substance.

**SODIUM PARA-AMINO BENZOATE.**— $NaC_7H_6O_2N$ .—M. W. 159.12.—The sodium salt of para-aminobenzoic acid.—Sodium *p*-aminobenzoate, when dried at 110° C. for three hours, contains not less than 98 per cent of  $NaC_7H_6O_2N$ .

Sodium *p*-aminobenzoate occurs as a white to a buff-colored, odorless, crystalline powder, possessing a saline taste. It is freely soluble in water, slightly soluble in alcohol, very slightly soluble in benzene and in chloroform, and practically insoluble in ether. An aqueous solution is alkaline to litmus paper.

Dissolve 2 Gm. of sodium *p*-aminobenzoate in 45 cc. of water, and add 5 cc. of diluted hydrochloric acid: a white flocculent, crystalline precipitate of *p*-aminobenzoic acid is formed. (Avoid the addition of excess hydrochloric acid which will redissolve the precipitate.) Filter by suction and reserve the filtrate for the heavy metals test listed below. Wash the precipitate twice with small portions of cold water, recrystallize from alcohol, filter and dry at 110° C.: the *p*-aminobenzoic acid so obtained melts between 186° and 189° C.

Dry about 2 Gm. of sodium *p*-aminobenzoate, accurately weighed, for three hours at 110° C.: the loss in weight does not exceed 7.5 per cent.

Dissolve 50 mg. of sodium *p*-aminobenzoate in 5 cc. of water; add, in order, 0.5 cc. of diluted hydrochloric acid, 0.5 cc. of tenth-molar sodium nitrite and 10 cc. of ammonia water containing 0.2 Gm. of *g*-naphthol: a red color develops.

Place 50 mg. of sodium *p*-aminobenzoate in a test tube containing 2 cc. of water and add, in order, 0.5 cc. of potassium iodide, T.S., 0.4 cc. of diluted hydrochloric acid, and 0.5 cc. of sodium hypochlorite T.S.: a heavy brown precipitate forms (*difference from p-aminohippuric acid*).

An aqueous solution (1 in 10) responds to the tests for sodium (*U. S. P. XIII*, p. 663).

Transfer about 1 Gm. of sodium *p*-aminobenzoate, dried and accurately weighed, to a 25 cc. Erlenmeyer flask containing 5 cc. of water and add 2 drops of phenolphthalein T.S.: no more than 0.5 cc. of fiftieth-normal sulfuric acid is required to discharge any pink color which may develop.

Transfer about 0.3 Gm. of sodium *p*-aminobenzoate, dried and accurately weighed, to a platinum crucible and ash to a white residue. Cool, add carefully a few drops of sulfuric acid and ignite to constant weight: the weight of the sulfated ash calculated as sodium sulfate is not less than 44.1 per cent nor more than 44.8 per cent.

A 0.2 Gm. sample of sodium *p*-aminobenzoate shows no more chloride than corresponds to 0.15 cc. of fiftieth-normal hydrochloric acid (*U. S. P. XIII*, p. 709). A 0.3 Gm. sample of sodium *p*-aminobenzoate shows no more sulfate than corresponds to 0.1 cc. of fiftieth-normal sulfuric acid (*U. S. P. XIII*, p. 709). The heavy metals limit (*U. S. P. XIII*, p. 657) of 25 cc. of the filtrate obtained previously in the melting point procedure is 20 p.p.m.

Transfer about 0.3 Gm. of sodium *p*-aminobenzoate, accurately weighed, to a 250 cc. beaker. Add 5 cc. of hydrochloric acid and 50 cc. of water. Mix to obtain complete solution, cool to 15° C., and add about 25 Gm. of crushed ice. Slowly titrate with tenth-molar sodium nitrite, previously standardized against sulfanilamide (*U. S. P. XIII*, p. 865), until a blue color is produced immediately when a glass rod dipped into the titrated solution is streaked on a smear of starch-iodide paste T.S. When the titration is complete, the end-point is reproducible after the mixture has been allowed to stand for one minute. Each cc. of tenth-molar sodium nitrite is equivalent to 0.01591 Gm. of sodium *p*-aminobenzoate: the sodium *p*-aminobenzoate content, calculated on the dry basis, is not less than 98 per cent nor more than 101 per cent.

### SODIUM PEROXIDE.— $\text{Na}_2\text{O}_2$ .—M. W. 77.99.

Sodium peroxide occurs in the form of a white or yellowish, amorphous powder. It is soluble in water (*caution!*), with decomposition and evolution of heat, forming an alkaline solution and liberating oxygen. It dissolves in cold dilute acids, forming a solution of hydrogen peroxide. When heated, sodium peroxide becomes darker, but on cooling resumes its original color. It does not react with alcohol, but it ignites ether on contact. A mixture with red phosphorus explodes under pressure on being struck. It is an extremely powerful oxidizing agent.

Sodium peroxide should not respond to tests for sulfates, chlorides, phosphates, nitrates and heavy metals. If 1 Gm. or 1.5 Gm. of sodium peroxide is weighed and gradually added with constant stirring to 950 cc. of 1 per cent sulfuric acid and the solution made up to 1,000 cc., the titration of 100 cc. of this solution with tenth normal potassium permanganate will indicate the presence of not less than 90 per cent sodium peroxide.

*Caution*—Sodium peroxide yields spontaneously explosive mixtures with many organic substances and the dry material may react violently with moist air.

### SODIUM RICINOLEATE SOLUTION.— $\text{C}_{18}\text{H}_{33}\text{O}_3\text{Na}$ .—M. W. 320.45.—A sterile, aqueous solution containing 2 Gm. of purified sodium ricinoleate per 100 cc.

Sodium ricinoleate solution, 2 per cent, occurs as a clear, odorless, pale yellow liquid. The  $\text{pH}$  is not less than 8.2 nor more than 8.5.

Transfer 50 cc. of sodium ricinoleate solution, 2 per cent, to a suitable separatory funnel, acidify with diluted sulfuric acid and extract with chloroform, using 25 cc., 20 cc., 20 cc., 15 cc. and 10 cc. portions, respectively. Filter the combined chloroform extracts through a pledget of

cotton into a tared beaker. Evaporate the chloroform to dryness on a steam bath, dry the residue at 100° C. for one hour, and weigh: the residue calculated to sodium ricinoleate should be not less than 0.018 Gm. and not more than 0.022 Gm. per cc.

**SODIUM TETRADECYL SULFATE.**— $C_{14}H_{29}SO_4Na$ .  
—M. W. 316.43.—Sodium-2-methyl-7-ethylundecyl sulfate-4.

Sodium tetradecyl sulfate occurs as a white, waxy, odorless solid. It is soluble in water, alcohol and ether. A 5 per cent aqueous solution is clear and colorless. The pH of a 5 per cent solution ranges from 6.5 to 9.0.

Add 3 drops of 5 per cent sodium tetradecyl sulfate solution to 1 cc. of ortho-phenanthroline T.S.: an orange-red precipitate forms.

Dissolve 1 Gm. of sodium tetradecyl sulfate in 20 cc. of water and make up to 25 cc., transfer to a 50 cc. Nessler tube. Add 10 cc. of hydrogen sulfide T.S. and allow to stand ten minutes: no more color develops than corresponds to 20 p.p.m. of lead (*U. S. P. XIII*, p. 657).

Dry 2 Gm. of sodium tetradecyl sulfate, accurately weighed, in a vacuum desiccator for 48 hours: the loss in weight is not more than 10 per cent. Weigh, accurately, 1 Gm. of sodium tetradecyl sulfate into a tared platinum dish, add 2 cc. of sulfuric acid, and heat gently to avoid spattering until no more fumes of sulfur trioxide are evolved. Repeat this treatment twice, then ignite and weigh. The sulfated ash content is not less than 19 per cent nor more than 25 per cent.

Weigh, accurately, about 0.3 Gm. of sodium tetradecyl sulfate into a suitable flask. Add 2 drops of bromocresol purple T.S., and neutralize with tenth-normal hydrochloric acid. Add slowly, with shaking, 25 cc. of a five-hundredths molar benzidine hydrochloride. Shake well and allow to stand at room temperature for one hour. Filter with suction. Test the filtrate for completeness of precipitation. Wash the precipitate with distilled water until the washings are neutral. Dissolve the precipitate by washing 4 times with hot 95 per cent alcohol previously neutralized to bromocresol purple T.S. Titrate the hot alcoholic solution with five-hundredths normal sodium hydroxide using bromocresol purple T.S. as the indicator. Each cc. of five-hundredths normal sodium hydroxide is equivalent to 0.0158 Gm. of sodium tetradecyl sulfate. The sodium tetradecyl sulfate found is not less than 85 per cent.

**STIBAMINE GLUCOSIDE.** —  $C_{36}H_{49}O_{22}N_3Sb_3Na$ . — F. W. 1264.05.—A nitrogen glucoside of sodium *p*-aminophenylstibonate.—A product of incompletely defined structure prepared by the condensation of *p*-aminophenylstibonic acid and glucose in a slightly basic solution, followed by precipitation with absolute alcohol and final drying. The rational formula provisionally assigned to stibamine glucoside is based upon the assumption of a trimer linked through the stibonic group.

Stibamine glucoside occurs as an odorless, pale cream to light buff colored, amorphous powder. It is soluble in water. The pH of a 6 per cent solution is from 8.5 to 9.0.

Heat 0.5 Gm. of stibamine glucoside dissolved in sodium carbonate solution: the vapors do not turn moist red litmus paper blue (*distinction from ethylstibamine which turns red litmus blue*).

Acidify the solution remaining after the assay for total antimony and saturate it with hydrogen sulfide: an orange colored precipitate is formed.

Dissolve 0.1 Gm. of stibamine glucoside in 5 cc. of water, add 5 cc. of 10 per cent sodium carbonate solution, and extract with 20 cc. of ether. Wash the ether extract with 10 cc. of water and extract with 5 cc. of diluted hydrochloric acid. To the acid extract add 0.1 cc. of tenth-normal sodium nitrite solution, allow to stand one minute, and add two drops of 1 per cent sulfamic acid and one drop of 0.1 per cent naphthylethylenediamine: no more color develops than is produced by similarly treating 0.1 mg. of aniline.

Acidify the extracted sodium carbonate solution with diluted hydrochloric

acid. Add two drops of sodium nitrite solution, and pour into a freshly prepared alkaline solution of "H" acid (1-amino-8-naphthol-3,6-disulfonic acid): a cherry-red color results.

Dry 0.5 Gm. of stibamine glucoside at 100 C. for 6 hours in a vacuum dryer at a pressure not above 5 mm. of mercury: the loss in weight is not over 8 per cent.

The nitrogen content of dry stibamine glucoside as determined by the Kjeldahl method is not less than 1.75 nor more than 2 per cent.

Transfer 0.2 Gm. of stibamine glucoside, accurately weighed, to a 500 cc. glass-stoppered iodine flask. Add 3.0 Gm. of finely powdered potassium permanganate and mix the two powders well by swirling the flask. Add 15 cc. of cool 50 per cent (V/V) sulfuric acid, allowing the acid to run into the flask in such a manner that the acid does not come in contact with the mixed powder (*caution!*). After the complete addition of the 50 per cent sulfuric acid, mix the acid with the powder by swirling the flask and allow to stand until all frothing ceases. Add 15 cc. of sulfuric acid in small portions, rotating the flask after each addition of acid (*caution!*). Allow to stand until all frothing ceases. Place on a hot plate and warm gently until frothing begins. Immediately add 20 cc. of distilled water, adding it so as to wash down the walls of the flask. Heat on the hot plate for 20 to 30 minutes in such manner that the mixture simmers, rotating the flask occasionally. Add 20 cc. of distilled water and then add to the simmering mixture small portions of saturated solution of oxalic acid until a colorless liquid is obtained. Add a saturated solution of potassium permanganate drop by drop until a permanent pink color remains. Remove the pink color by adding diluted oxalic acid solution drop by drop. Dilute the mixture to about 150 cc. with distilled water, heat to boiling, remove from the hot plate and cool to 15-20 C. Add 2.5 Gm. of potassium iodide and immediately stopper and rotate the flask until the potassium iodide is dissolved. Place the flask in a dark place and allow to stand for one hour. Titrate with tenth-normal sodium thiosulfate until 7 cc. have been added and a pale yellow color is reached. Add about 150 cc. of distilled water, 3 cc. of one per cent starch solution and titrate until the disappearance of the blue color.

Perform a blank determination in the same manner employing all reagents except the assay sample. Before beginning the titration with tenth-normal sodium thiosulfate, add about 150 cc. of water and 6 cc. of starch T.S. The blank should require no more than 0.4 cc. of tenth-normal sodium thiosulfate; the exact amount is deducted from the principal titration figure. Each cc. of tenth-normal sodium thiosulfate is equivalent to 6.09 mg. of antimony. The amount of antimony found is equivalent to not less than 24 per cent nor more than 27 per cent, calculated to the dried substance.

**STILPALMITATE.**— $C_{50}H_{80}O_4$ .—M. W. 745.14.—Diethylstilbestrol dipalmitate.—The dipalmitic acid ester of diethylstilbestrol.

Stilpalmitate occurs as a white to yellowish odorless, waxy, crystalline powder. It is practically insoluble in water; slightly soluble in alcohol; sparingly soluble in fatty oils at room temperature, but dissolves more freely on warming; and soluble in ether and chloroform. It melts between 81° and 85° C.

Dry about 0.25 Gm. of stilpalmitate over concentrated sulfuric acid in a vacuum desiccator for 24 hours: the loss in weight is not more than 0.1 per cent.

Transfer about 13.85 mg. of stilpalmitate, accurately weighed, to a 125 cc. Erlenmeyer flask. Add 10 cc. of alcohol and 3 drops of concentrated sulfuric acid. Hydrolyze in a boiling water bath under a reflux condenser for two hours. Transfer the solution quantitatively to a 100 cc. volumetric flask and make up to volume with alcohol. To 5 cc. of this hydrolyzed solution placed in a 100 cc. volumetric flask, add 5 cc. of distilled water, 2 cc. of diluted hydrochloric acid, 4 cc. of molybdophosphotungstate T.S. (U. S. P.) and 50 cc. of distilled water. Allow to stand for ten minutes, then add 10 cc. of a 25 per cent aqueous solution of anhydrous sodium carbonate; dilute to exactly 100 cc., mix well and allow to stand for 45 minutes. Filter the solution through a dry



filter, rejecting the first portion of the filtrate. Treat a 5 cc. portion of diethylstilbestrol standard solution (10 mg. of diethylstilbestrol U. S. P. Reference standard in alcohol to make 200 cc.) with the same quantities of reagents and in the same manner as the sample being tested. Treat a 5 cc. portion of alcohol in the same manner. This constitutes the blank. Determine the optical density of the solutions in a suitable photoelectric colorimeter or spectrophotometer at a wavelength of about 5,500 Å, using the blank to obtain 100 per cent transmission. Calculate the quantity of diethylstilbestrol represented in the unknown: the diethylstilbestrol content of the stilpalmitate is not less than 34.5 per cent nor more than 37.5 per cent.

**SULFAPYRAZINE.**— $C_{10}H_{10}N_4O_2S$ .—M. W. 250.27.—*p*-Amino-N-2-pyrazinylbenzenesulfonamide.

Sulfapyrazine occurs as an odorless, tasteless, white or yellowish white, crystalline powder, which may darken on exposure to light. It is soluble in aqueous solutions of sodium, potassium and barium hydroxide, in ammonium hydroxide and in dilute and concentrated mineral acid solutions; practically insoluble in ether and chloroform; very slightly soluble in alcohol; slightly soluble in acetone and practically insoluble in water (5 mg. per 100 cc. at 25° C., and 5.2 mg. per 100 cc. at 37° C.). The melting point of sulfapyrazine is 250-254° C. with decomposition.

Place about 0.5 Gm. of sulfapyrazine in a test tube, wrap the upper part of the test tube with wet filter paper and heat the lower part in a bath at 230-250° C.: a white, crystalline sublimate collects in the top of the tube. The fumes evolved during the decomposition possess no odor of ammonia and little or no odor of hydrogen sulfide; the melted sulfapyrazine first appears reddish brown, then chars. (*On heating, sulfanilamide produces a violet blue residue and the odors of ammonia and aniline; Sulfapyridine produces a brown residue and the odor of sulfur dioxide; sulfathiazole produces a brown to red residue and odors of ammonia, aniline and hydrogen sulfide; sulfadiazine and sulfamerazine produce a reddish brown residue but no hydrogen sulfide; or ammonia; sulfaguandinine produces a purple to violet residue and the odor of ammonia.*) The crystalline 2-amino-pyrazine obtained by pyrolysis (and found on the cool sidewalls of the test tube) melts sharply at 120-122° C. (*distinction from other sulfonamides except sulfadiazine which gives a sublimate melting sharply at 126-127° C. when purified. Sulfamerazine gives a sublimate melting sharply at 159-161° C. when purified.*).

To 0.1 Gm. of sulfapyrazine add 0.5 cc. of tenth-normal sodium hydroxide and dilute to 10 cc. with distilled water. Add five drops of cupric sulfate T.S.: a light pea green precipitate forms which becomes white on standing (*distinction from sulfapyridine, which forms an apple green precipitate that turns olive green; from sulfadiazine, which forms an olive green precipitate changing to purple gray on standing; from sulfamerazine, which gives an olive green precipitate changing to dark gray on standing; from sulfathiazole, which forms a violet precipitate; from sulfaguandinine, which forms a dark brown precipitate; and from sulfanilamide, which forms no precipitate or a light blue one.*).

Digest 2.0 Gm. of sulfapyrazine with 100 cc. of distilled water at about 70° C. for five minutes; cool and filter. (1) To 25 cc. of filtrate add two drops of phenolphthalein T.S. and titrate with tenth-normal sodium hydroxide: not more than 0.1 cc. of sodium hydroxide is required to produce a pink color. (2) To another 25 cc. of the filtrate add 1 cc. of nitric acid and 1 cc. of silver nitrate T.S.; mix well and allow to stand five minutes protected from direct sunlight: the turbidity does not exceed that produced in a control test made with 0.1 cc. of fiftieth-normal hydrochloric acid. (3) To another 25 cc. of the filtrate add 1 cc. of dilute hydrochloric acid and 1 cc. of barium chloride T.S.; mix well and allow to stand ten minutes: the turbidity does not exceed that produced in a control test made with 0.2 cc. of fiftieth-normal sulfuric acid.

Dissolve 0.5 Gm. of sulfapyrazine in a mixture of 5 cc. of sodium hydroxide T.S. and 20 cc. of distilled water: the solution is clear

and not more than pale yellow in color; add five drops of freshly prepared sodium sulfide T.S.: the darkening produced does not exceed that developed in a control test to which has been added 0.01 mg. of lead.

Dry an accurately weighed specimen of sulfapyrazine at 100° C. for 24 hours: the loss in weight does not exceed 0.2 per cent.

Ignite about 1 Gm. of sulfapyrazine, accurately weighed. Cool, add sufficient sulfuric acid to moisten the charred mass and ignite to constant weight: the ash is not more than 0.1 per cent.

Dissolve about 0.5 Gm. of sulfapyrazine in 10 cc. of distilled water and 10 cc. of hydrochloric acid contained in a 250 cc. beaker, dilute to 50 cc., cool to 15° C., and titrate with tenth-molar sodium nitrite. The endpoint is the first blue streak obtained immediately when a glass rod dipped into the solution is drawn across a smear of starch-iodide paste on white filter paper (or on a clear glass plate). The solution should retain this endpoint for 30 seconds. Each cc. of tenth-molar sodium nitrite corresponds to 0.02503 Gm. of anhydrous sulfapyrazine: the amount of sulfapyrazine found corresponds to not less than 99.0 per cent nor more than 101.0 per cent.

**SULFAPYRAZINE SODIUM.**— $C_{10}H_9N_4NaO_2S \cdot H_2O$ .—M. W. 290.28.—The monohydrated sodium salt of 2-sulfanilamidopyrazine.

Sulfapyrazine sodium occurs as a white, odorless, bitter tasting powder, which darkens on exposure to light. It is freely soluble in water (1 Gm. in 3.33 cc. at 25° C.), very soluble in acetone, slightly soluble in alcohol; and insoluble in ether and chloroform. Aqueous solutions of sulfapyrazine sodium may absorb carbon dioxide to cause precipitation of sulfapyrazine. The pH of a 10 per cent solution is 9.1.

Dissolve 2 Gm. of sulfapyrazine sodium in 90 cc. of distilled water, add 10 cc. of acetic acid and filter. Separate 25 cc. portions of the filtrate meet the requirements for chloride and for sulfate given under Sulfapyrazine-N. N. R. Wash the residue with distilled water and dry at 100° C.: the dry precipitate meets the tests for identification given under Sulfapyrazine-N. N. R.

Dissolve 0.5 Gm. of sulfapyrazine sodium in 25 cc. of distilled water: the solution is clear, not more than a pale yellow, and meets the requirements for heavy metals given under Sulfapyrazine-N. N. R.

Dry an accurately weighed portion of sulfapyrazine sodium at 110° C. for four hours: the loss in weight is not less than 6.1 per cent nor more than 6.4 per cent. Ash 0.2 Gm. of anhydrous sulfapyrazine sodium, accurately weighed, with the addition of 0.5 cc. of sulfuric acid. Ignite until the carbon residue has been burned off, add 0.5 cc. of sulfuric acid, heat gently to drive off the excess acid, and ignite to constant weight: the weight of sodium sulfate formed is not less than 24.8 per cent nor more than 26.2 per cent.

Dissolve about 0.5 Gm. of anhydrous sulfapyrazine sodium, accurately weighed, in 10 cc. of distilled water and 20 cc. of hydrochloric acid contained in a 250 cc. beaker, dilute to 50 cc., cool to 15° C., and titrate with tenth-molar sodium nitrite. The endpoint is the first blue streak obtained immediately when a glass rod dipped into the solution is drawn across a smear of starch-iodide paste on white filter paper (or on a clear glass plate). The solution should retain this endpoint for 30 seconds. Each cc. of tenth-molar sodium nitrite corresponds to 0.02723 Gm. of anhydrous sulfapyrazine sodium: the amount of sulfapyrazine sodium found corresponds to not less than 99.0 per cent nor more than 101.0 per cent.

**THEOBROMINE CALCIUM SALICYLATE.**— $C_{14}H_{12}CaN_4O_5$ .—F. W. 356.35.—A double salt or mixture of calcium theobromine ( $[C_7H_7O_2N_4]_2Ca$ ) and calcium salicylate ( $[C_7H_5O_3]_2Ca$ ). It contains not less than 44 per cent of theobromine.

Theobromine calcium salicylate is a white, amorphous powder, with a saline taste. It is partly soluble in water. An aqueous solution of theobromine calcium salicylate is alkaline to phenolphthalein.

An aqueous solution of theobromine calcium salicylate (1 in 100), slightly acidified with 3 per cent acetic acid, becomes violet on the addition of ferric chloride T.S. Transfer about 0.05 Gm. of theobromine calcium salicylate to a test tube, add 3 cc. of diluted acetic acid and heat to boiling; cool the contents of the test tube, filter and to the filtrate add 0.5 cc. of ammonium oxalate T.S.: a precipitate forms, which dissolves on addition of 1 cc. of diluted hydrochloric acid. To about 0.05 Gm. of the precipitate obtained in the assay for theobromine, add 1 cc. of hydrochloric acid and about 0.1 Gm. of potassium chlorate and evaporate to dryness on a water bath: a reddish yellow residue remains, which becomes purple when moistened with a drop of diluted ammonia solution.

Dried to constant weight at 110° C., theobromine calcium salicylate loses not more than 5 per cent in weight (*water*). Treat 0.1 Gm. of theobromine calcium salicylate with 2 cc. of sulfuric acid: no effervescence occurs (*carbonate*) nor is more than a slight color produced (*readily carbonizable substances*). Mix 1 Gm. of theobromine calcium salicylate with 10 cc. of distilled water, add a few cubic centimeters of sodium hydroxide T.S. (filter if necessary) and shake the mixture with 10 cc. of chloroform. Separate the chloroform layer, evaporate it to dryness on a water bath and dry to constant weight at 80 C.: the weight of the residue so obtained does not exceed 0.005 Gm. (*caffeine*).

Suspend about 2 Gm. of the salt, accurately weighed, in 75 cc. of water and add diluted hydrochloric acid until the solution is acid to phenolphthalein. Warm gently, then add sodium carbonate T.S. until the calcium is completely precipitated, avoiding a large excess. Filter off the calcium carbonate; evaporate the combined filtrate and washings on a steam bath to 20 cc. Add diluted hydrochloric acid, drop by drop, until just acid (to phenolphthalein), then diluted ammonia solution until slightly alkaline. Allow to stand at 20° to 25° C. for three hours, stirring occasionally. Transfer the precipitate of theobromine to a tared Gooch crucible. Wash the precipitate and filter with four successive 5 cc. portions of ice cold distilled water and dry to constant weight at 100 C. To the weight of the precipitate thus obtained, add 0.14 Gm. The total weight corresponds to not less than 44 per cent of the weight of the sample taken. About 0.2 Gm. of the precipitate obtained in the assay for theobromine volatilizes when slowly heated, leaving only a negligible residue.

**THEOPHYLLINE-METHYLGLUCAMINE.**—An equimolecular mixture of Theophylline-U. S. P. ( $C_7H_8N_4O_2 \cdot H_2O$ ) and methylglucamine ( $C_7H_{17}NO_5$ ). Dosage forms of theophylline-methylglucamine contain not less than 95 per cent nor more than 105 per cent of the labeled quantities of theophylline and methylglucamine.

Transfer a portion of powdered tablets or of solution, equivalent to approximately 0.35 Gm. of theophylline-methylglucamine to a separatory funnel. Add 25 cc. of water and 2 drops of methyl red T.S., and titrate to a faint red color with tenth-normal hydrochloric acid. Each cc. of tenth-normal hydrochloric acid is equivalent to 19.52 mg. of methylglucamine. The amount of methylglucamine found is not less than 95 per cent nor more than 105 per cent of the labeled amount of methylglucamine.

To the mixture that has been titrated in the separatory funnel, add 4 drops of tenth-normal hydrochloric acid and extract with 4 portions of 25 cc., 20 cc., 15 cc., and 15 cc. of a mixture of three volumes of chloroform and one volume of isopropyl alcohol. Filter the extract through a small dry filter paper into a dried and tared evaporating dish. Wash the filter with a small amount of the extraction solvent and evaporate the combined extract and washings on a water bath. Dry the residue to constant weight at 100° C.: the weight of the residue, multiplied by 1.100, is equivalent to not less than 95 per cent nor more than 105 per cent of the labeled amount of theophylline—U. S. P.

The theophylline employed in theophylline-methylglucamine preparations meets the requirements of the United States Pharmacopeia.

**METHYLGLUCAMINE** ( $C_7H_{17}NO_5$ —M. W. 195.2) occurs as white to yellowish-white, odorless crystals which melt from 128-131° C. It is freely soluble in water, slightly soluble in alcohol, and practically insoluble in chloroform and in ether.

To 5 cc. of 5 per cent methylglucamine solution add 5 cc. of alkaline cupric tartrate T.S. and heat to boiling: no reduction of copper occurs (*absence of reducing substances*).

Dry about 1.0 Gm. of methylglucamine to constant weight at 100° C.: the loss of weight is not more than 0.1 per cent.

The specific rotation,  $[\alpha]_{25/D}$ , of a 10 per cent solution of methylglucamine in water is approximately — 16.3°.

Ignite about 1.0 Gm. of methylglucamine, accurately weighed: the ash is negligible.

Dissolve 1 Gm. of methylglucamine in 25 cc. of water: the heavy metals limit (*U. S. P. XIII*, p. 657) is 20 p.p.m.

The nitrogen content of methylglucamine when determined by the Dumas method, is not less than 7.0 per cent nor more than 7.2 per cent.

Transfer about 0.4 Gm. of methylglucamine, accurately weighed, to an Erlenmeyer flask and add 25 cc. of water and 2 drops of methyl red T.S. Titrate the mixture with tenth-normal hydrochloric acid. Each cc. of tenth-normal hydrochloric acid is equivalent to 19.52 mg. of methylglucamine. The amount of methylglucamine found is not less than 98 per cent, calculated to the dry substance.

### THIOUREA.— $CH_4N_2S$ .—M. W. 76.12.

Thiourea is a white, crystalline, almost odorless solid. It is slightly soluble in cold alcohol and very slightly soluble in chloroform and ether. When 50 mg. is dissolved in 10 cc. of water to which 2 drops of ferric chloride T.S. have been added, the color is only slightly deepened (*sulfocyanates*). Warm 50 mg. of thiourea in a test tube until it melts, cool, add 10 cc. of water and 2 drops of ferric chloride solution: a blood red color results. Add 10 cc. of water and 4 cc. of diluted nitric acid to a mixture of 0.1 Gm. bismuth nitrate and 0.3 Gm. of thiourea, and warm: an orange colored solution results, which upon evaporation yields orange crystals. The melting point of thiourea ranges from 176° to 180° C.

**THROMBIN, TOPICAL.**—Thrombin.—A preparation of thrombin, isolated from bovine or human plasma.

The product supplied by Parke, Davis, a mixture of thrombin (*bovine*) and sucrose is a white powder, completely soluble in water or isotonic solution of sodium chloride. It contains not more than 1 mg. of protein nitrogen per 300 units of thrombin. When dried over phosphorus pentoxide under vacuum for 48 hours at room temperature the loss in weight is not greater than 1 per cent. The ash content is not more than 5 mg. per thousand units of thrombin. When heated in an oven at 50° C. for two weeks, the product shows no loss in activity.

**TRIMETHADIONE.**— $C_6H_9NO_3$ .—M. W. 143.14.—3,5,5-Trimethyloxazolidine-2,4-dione.

Trimethadione occurs as a white, granular, crystalline substance possessing a slight camphor-like odor. It melts at 45-46.5° C. It is soluble in water and freely soluble in alcohol, benzene, chloroform and ether. The pH of a 5 per cent solution is about 6.0.

Add 1 cc. of one-normal barium hydroxide to 5 cc. of a 2 per cent aqueous solution of trimethadione: within a few seconds a considerable precipitate appears.

Add 3 cc. of 25 per cent sodium hydroxide to 0.5 Gm. of trimethadione. Heat for thirty minutes on a boiling water bath. Carefully evaporate the solution to 0.5 cc. over a free flame, during the course of which a heavy precipitate forms. Cool and carefully treat the residue with hydrochloric acid until the resulting solution is acid to litmus. Add 1 drop of ferric

chloride T.S. to 10 drops of the aforementioned solution: a deep yellow color develops.

Extract the acid solution obtained as described in the preceding paragraph with three 10 cc. portions of ether. Decant the ether extracts from the residue and combine all three ether fractions. Evaporate the ether solution to dryness on the steam bath and then recrystallize from benzene: the melting point of the crystals is 79-81 C.

Accurately weigh about 10 mg. of the product obtained as described in the previous paragraph. Transfer to a 150 cc. beaker, add 3 drops of alcohol to effect solution and follow with about 25 cc. of water. Add two drops of phenolphthalein T.S. and titrate with one-hundredth normal sodium hydroxide: the neutralization equivalent is within the limits 101-107.

Dry 0.5 Gm. of trimethadione, accurately weighed, over phosphorus pentoxide for six hours: the loss does not exceed 0.1 per cent.

Ash about 1.0 Gm. of trimethadione, accurately weighed: the amount of residue is not more than 0.05 per cent.

Weigh accurately about 0.2 Gm. of trimethadione. Dissolve it in about 5 cc. of alcohol and then add 25 cc. of water followed by 25 cc. of tenth-normal sodium hydroxide. Allow to stand for 15 minutes, add 4 drops of cresolphthalein indicator solution and titrate the excess alkali with tenth-normal hydrochloric acid. Each cc. of tenth-normal sodium hydroxide is equivalent to 0.014314 Gm. of trimethadione: the trimethadione content is not less than 98 per cent nor more than 102 per cent.

**TRIMETHADIONE CAPSULES:** Weigh sufficient powder from ten capsules to obtain about 100 mg. of trimethadione. Transfer to a small beaker, add 5 cc. of 95 per cent alcohol and allow to stand for five minutes. Decant the alcohol through filter paper previously moistened with alcohol. Repeat the extraction with alcohol and the filtration twice more. Dilute the combined filtrates to four times their original volume with water. Add 20 cc. of tenth-normal sodium hydroxide to the solution and allow it to stand for five minutes; add two drops of cresolphthalein and then neutralize the excess alkali with tenth-normal hydrochloric acid. Each cc. of tenth-normal sodium hydroxide is equivalent to 0.014314 Gm. of trimethadione: the trimethadione content is not less than 95 per cent nor more than 105 per cent of the claimed amount.

**TRIMETHADIONE SOLUTION:** Pipette 2 cc. of trimethadione solution (about 40 mg. per cc.), add 50 cc. of water and then 20 cc. of tenth-normal sodium hydroxide. Allow the trimethadione to hydrolyze for five minutes, add two drops of cresolphthalein indicator solution and titrate the excess alkali with tenth-normal hydrochloric acid. Each cc. of tenth-normal sodium hydroxide used is equivalent to 0.014314 Gm. of trimethadione: the trimethadione content is not less than 97.5 per cent nor more than 102.5 per cent of the claimed amount.

**TRIPLENNAMINE HYDROCHLORIDE.**— $C_{16}H_{21}N_3 \cdot HCl$ .—M. W. 291.84.—N,N-dimethyl-N'-benzyl-N'-( $\alpha$ -pyridyl)ethylenediamine hydrochloride.

TripeleNNamine hydrochloride occurs as a white crystalline powder possessing a bitter taste. It melts in the range 189-192.5° C. It is very soluble in water, soluble in alcohol and chloroform, and practically insoluble in benzene and ether. The  $pH$  of a 10 per cent solution is from 6.4 to 6.6.

Acidify 2 cc. of a 1 per cent solution of tripeleNNamine hydrochloride with 2 drops of nitric acid. Add 5 drops of silver nitrate T.S.: a white precipitate develops, which is redissolved on the addition of a few drops of strong ammonia solution.

Add 3 drops of saturated Reinecke's salt solution to 2 cc. of a 1 per cent aqueous solution of tripeleNNamine hydrochloride: a flocculent, pink precipitate develops.

Prepare the dipicrate of tripeleNNamine as described in the assay for tripeleNNamine: the tripeleNNamine dipicrate melts at (*caution!*) 185-190° C.

Add 3 cc. of sulfuric acid to 0.1 Gm. of tripeleNNamine hydrochloride:

a yellow color develops which turns muddy brown with a definite greenish cast on standing (*distinction from benadryl hydrochloride*).

Dry 0.2 Gm. of tripeleannamine hydrochloride, accurately weighed, in vacuum over phosphorus pentoxide at room temperature for 24 hours: the loss in weight does not exceed 0.5 per cent.

Ash about 0.2 Gm. of tripeleannamine hydrochloride, accurately weighed: the amount of residue is not more than 0.3 per cent.

Weigh, accurately, about 100 mg. of tripeleannamine hydrochloride and transfer to a 100 cc. beaker. Dissolve the salt in 50 cc. of water to which 4 drops of sulfuric acid has been added and add slowly, while stirring, 25 cc. of a filtered saturated solution of picric acid. Allow the mixture to stand for two hours, filter through a tared Gooch crucible, dry at 100° C. for two hours, cool and weigh. Each gram of tripeleannamine dipicrate is equivalent to 0.40896 Gm. of tripeleannamine hydrochloride: the tripeleannamine hydrochloride content is not less than 98 per cent nor more than 102 per cent.

**TUAMINE-Lilly.**— $C_7H_{17}N$ .—M. W. 115.22.—*d,l*-2-Aminoheptane.

Tuamine occurs as a colorless to pale yellow liquid which boils within the range 138.5-142.5° C. It is sparingly soluble in water but freely soluble in alcohol, benzene, chloroform and ether.

At 25° C. Tuamine exhibits a refractive index from 1.4150 to 1.4200, a specific gravity from 0.7600 to 0.7660 and a vapor pressure of approximately 4.8 mm. of mercury. The pH of a 1 per cent solution of Tuamine is 11.45.

Dissolve 1 cc. of Tuamine and 1 Gm. of potassium cyanate in 25 cc. of distilled water to which 5 cc. of 10 per cent sulfuric acid has been added. Warm the solution on a steam bath for one hour; cool, filter, wash with distilled water and dry the crystals at 100 C.: the product melts at 127-129° C.

Transfer about 1 cc. of Tuamine to a tared weighing bottle and weigh it accurately. Evaporate the Tuamine on a steam bath to constant weight: the nonvolatile residue does not exceed 0.2 per cent. Dissolve 1 cc. of Tuamine in 10 cc. of liquid petrolatum, U. S. P.; no turbidity is produced.

Weigh accurately about 1 Gm. of Tuamine and dissolve it in 25 cc. of half-normal sulfuric acid. Titrate the excess acid with half-normal sodium hydroxide, using methyl red T.S. as the indicator. Each cc. of half-normal sulfuric acid is equivalent to 0.0576 Gm. of Tuamine: the Tuamine content is not less than 99.0 per cent.

**TUAMINE INHALER.**—Transfer the contents of the inhaler to an ammonia distillation flask and rinse the container with water, adding the washings to the flask. Add 3 cc. of 40 per cent sodium hydroxide and distil the amine into 35 cc. of tenth-normal hydrochloric acid. Complete the determination as directed under Tuamine. Each cubic centimeter of tenth-normal hydrochloric acid is equivalent to 0.01152 Gm. of Tuamine: the amount of Tuamine found is not less than 95 per cent nor more than 105 per cent of the amount claimed to be present at the time of packaging.

**TUAMINE SULFATE-Lilly.**— $C_{14}H_{34}N.H_2SO_4$ .—M. W. 328.51.—*d,l*-2-Aminoheptane sulfate.

Tuamine Sulfate occurs as a white, odorless powder, which is readily soluble in water. The pH of a 1 per cent solution is about 5.4.

Dry 1 Gm. of Tuamine Sulfate, accurately weighed, to constant weight at 100 C.: the loss in weight does not exceed 1 per cent.

Ignite about 0.5 Gm. of Tuamine Sulfate, accurately weighed: the amount of residue is not more than 0.1 per cent.

Dissolve 1.2 Gm. of Tuamine Sulfate in 25 cc. of water to which 1 Gm. of potassium cyanate has been added. Heat on a steam bath for one hour; cool, filter, wash the crystals with distilled water and dry at 100° C.: the derivative melts at 127-129° C.

Dissolve about 0.2 Gm. of Tuamine Sulfate, accurately weighed, in 100 cc. of distilled water; add 1 cc. of hydrochloric acid and heat;

add 20 cc. of barium chloride T.S. dropwise to the boiling solution. Allow the mixture to stand four hours and then filter through a previously tared Gooch crucible. Wash the precipitate until chloride-free, dry and finally ignite to constant weight: the weight of barium sulfate found is equivalent to a sulfate content of not less than 28.5 per cent nor more than 30 per cent.

The nitrogen content, as determined by the Dumas method, is not less than 8.35 per cent nor more than 8.75 per cent.

Dilute about 1 Gm. of Tuamine Sulfate, accurately weighed, with water to the mark of a 25 cc. volumetric flask. Transfer 5 cc. of the solution to an ammonia distillation apparatus; add 3 cc. of 40 per cent sodium hydroxide solution and distil the amine into 20 cc. of tenth-normal hydrochloric acid until 25 cc. of distillate has been collected. Titrate the acid solution with tenth-normal sodium hydroxide, using methyl red T.S. as the indicator. Each cc. of tenth-normal acid is equivalent to 0.01643 Gm. of Tuamine Sulfate: the 2-aminoheptane sulfate content is not less than 96.5 per cent.

**SOLUTION TUAMINE SULFATE 1 PER CENT AND 2 PER CENT.**—Use 25 cc. of the Tuamine Sulfate solution for the reaction with potassium cyanate as described in tests and standards for Tuamine: the product melts at 127-129° C.

Transfer 5 cc. of the solution to an ammonia distillation apparatus. Add 3 cc. of 40 per cent sodium hydroxide solution to the reaction chamber and distil the amine into 10 cc. of tenth-normal hydrochloric acid. Titrate the acid solution with tenth-normal sodium hydroxide, using methyl red as the indicator. Each cubic centimeter of tenth-normal hydrochloric acid is equivalent to 0.01643 Gm. of Tuamine Sulfate: the 2-aminoheptane sulfate content is not less than 95 per cent nor more than 105 per cent of the stated amount.

**d-TUBOCURARINE CHLORIDE.**— $C_{38}H_{44}Cl_2N_2O_6 \cdot 5H_2O$ .—M. W. 785.74.—The crystalline chloride of a quaternary base alkaloid obtainable from the bark and stems of *Chondrodendron tomentosum* and related species. *d*-Tubocurarine chloride is standardized biologically by the rabbit "head-drop" method.

The following statements constitute provisional tests and standards for *d*-tubocurarine chloride:

*d*-Tubocurarine chloride occurs as a colorless or yellowish-white to gray or light brown, odorless, crystalline powder. It is soluble in water, slightly soluble in alcohol, and practically insoluble in chloroform and ether. When previously dried at 100° C. for four hours, it melts with decomposition somewhere between 265° and 278° C., provided the melting point tube is placed in a bath preheated to 260° C.

Prepare a stock solution of 0.1 Gm. of *d*-tubocurarine chloride in 10 cc. of water: It is colorless or yellowish and free of insoluble material. Dilute 1 cc. of the stock solution to 100 cc. with water and to 2 cc. of this solution, add 3 cc. of Folin-Ciocalteu phenol reagent (*Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists*, ed. 6, p. 319), previously diluted (1:3) with water, and adjust the volume to 25 cc. with water. Add 2 cc. of 20 per cent sodium carbonate solution, mix, and heat the mixture for three minutes in a boiling water bath: a brilliant blue color develops.

Dilute 0.5 cc. of the stock solution with 10 cc. of water, add 0.2 cc. of sulfuric acid and 2 cc. of a 1 per cent potassium iodate solution, mix thoroughly and warm in a water bath for 30 minutes: a yellow color develops.

To 1 cc. of the stock solution add 1 cc. of a 4 per cent Reinecke's salt solution: a pink precipitate results. To 1 cc. of the solution add 1 cc. of saturated picric acid solution: a yellow precipitate results. To 1 cc. of the stock solution add 1 cc. of silver nitrate T.S.: a white precipitate forms, soluble in ammonia T.S.

Dry about 0.1 Gm. of *d*-tubocurarine chloride, accurately weighed, in a tared weighing bottle at 100° C. for four hours: the loss in weight does not exceed 11.5 per cent.

Transfer 0.2 Gm. of *d*-tubocurarine chloride, accurately weighed, to a separatory funnel containing 200 cc. of water. Add 5 cc. of saturated sodium bicarbonate solution and extract with three 20 cc. portions of chloroform. Wash the combined chloroform extracts with 10 cc. of water, filter through a pledget of cotton into a tared beaker, evaporate and dry at 100° C. for 1 hour: the weight of the residue does not exceed 3 per cent calculated on the dry basis. The residue is insoluble in water, but soluble in diluted hydrochloric acid.

Transfer about 0.15 Gm. of *d*-tubocurarine, accurately weighed, to a 100 cc. Erlenmeyer flask and add 10 cc. of water, 5 cc. of diluted nitric acid and exactly 25 cc. of fiftieth-normal silver nitrate. Add 5 cc. of nitrobenzene and swirl the contents of the flask to entrap the precipitate. Add 2 cc. of ferric ammonium sulfate T.S. and titrate the excess silver nitrate with fiftieth-normal ammonium thiocyanate. Each cc. of fiftieth-normal silver nitrate is equivalent to 0.000709 Gm. of chlorine: the chlorine content found is not less than 9.5 nor more than 10.2 per cent, calculated to the dry substance.

Transfer about 0.1 Gm. of *d*-tubocurarine chloride, accurately weighed, to a 10 cc. calibrated flask, dissolve the salt and make up to volume with water. Let the solution stand for three hours and determine the optical rotation in a 100 mm. polarimeter tube: the specific rotation,  $[\alpha]_{25/D}$ , calculated from the observed rotation and the concentration (expressed in grams of dried *d*-tubocurarine chloride per 100 cc. of solution) is not less than +208° nor more than +217°. (The most probable value of the specific rotation for pure anhydrous *d*-tubocurarine chloride is +215°.)

The potency of *d*-tubocurarine chloride is determined by observation of the "head-drop" response following intravenous injection of the drug in rabbits. (For assay methods see H. A. Holaday, U. S. Patent 2,397,417; R. F. Varney, C. R. Linegar and H. A. Holaday, *Federation Proc.*, 7, Part 1:261 (March) 1948; and G. M. Everett, *J. Pharmacol. & Exper. Therap.* 92:236 (March) 1948.)

**VINBARBITAL SODIUM.**— $C_{11}H_{15}N_2NaO_3$ .—M. W. 246.24.—The monosodium salt of 5-ethyl-5-(1-methyl-1-butenyl) barbituric acid.

Vinbarbital sodium occurs as a white, odorless powder, possessing a bitter taste. It is soluble in alcohol and water and slightly soluble in ether and chloroform. A 1 per cent aqueous solution is alkaline to phenolphthalein and has a *pH* between 8.5 and 9.5.

Unbuffered aqueous solutions of vinbarbital sodium are not stable. The powder is hygroscopic and if capsules containing it are broken or exposed to high humidity the contents are affected by both moisture and carbon dioxide.

To 5 cc. of a 10 per cent solution of vinbarbital sodium slowly add 2 cc. of diluted hydrochloric acid; allow the precipitate to crystallize; filter, wash and dry at 90° C.: the melting point of the vinbarbital is 161° to 168° C.

Transfer 5 cc. portions of a 10 per cent solution of vinbarbital sodium to two test tubes and to one add 1 cc. of mercuric bichloride T.S.: a white precipitate results, soluble in 10 cc. of diluted ammonia solution; to the other portion add 5 cc. of silver nitrate T.S.: a white precipitate results, soluble in 5 cc. of strong ammonia solution.

Dissolve 0.1 Gm. of vinbarbital sodium in 10 cc. of distilled water, add 1 cc. of sodium hydroxide T.S. and 4 drops of potassium permanganate T.S.: a green color develops in 20 seconds; add 5 cc. of diluted hydrochloric acid: the solution turns pink and a brown precipitate appears. Boil 0.5 Gm. of vinbarbital sodium with 5 cc. of 25 per cent sodium hydroxide: ammonia is evolved.

Acidify 40 cc. of a 10 per cent solution of vinbarbital sodium with diluted nitric acid and filter; separate portions of 20 cc. each of the filtrate yield no opalescence with 1 cc. of silver nitrate T.S. (*chloride*); no turbidity with 1 cc. of barium nitrate T.S. (*sulfate*); no color or precipitate on saturation with hydrogen sulfide (*salts of heavy metals*).

Transfer about 3 Gm. of vinbarbital sodium, accurately weighed, to a glass stoppered flask, add 50 cc. of anhydrous ether and shake for ten minutes. Decant the supernatant liquid through a filter and again



extract the residue with 15 and 10 cc. portions of ether. Evaporate the combined filtered extracts to dryness in a tared beaker on the steam bath: the residue does not exceed 0.5 per cent.

Transfer about 0.5 Gm. of vinbarbital sodium, accurately weighed, to a separatory funnel, add 30 cc. of water and 10 cc. of diluted hydrochloric acid. Extract with seven successive portions of ether, filter the combined extracts and evaporate in a tared dish in a warm stream of air: the 5-ethyl-5-(1-methylbutenyl)barbituric acid content is not less than 89.5 per cent nor more than 92 per cent. Evaporate the aqueous residue to dryness, add 3 cc. of sulfuric acid and evaporate the excess acid. Repeat, using 1 cc. of acid and ignite the residue: the sulfated ash is not less than 27.5 nor more than 29.5 per cent.

**VITAMIN D<sub>2</sub>.—C<sub>28</sub>H<sub>44</sub>O.**—M. W. 396.63.—9,10-Ergosta-tetraene (18:10, 5:6, 7:8, 22:23)-ol-3.

Vitamin D<sub>2</sub> may be prepared by ultraviolet irradiation of ergosterol in a suitable solvent or by electronic bombardment of the compound: it is not identical with the vitamin D which predominates in fish liver oils and which is called vitamin D<sub>3</sub>. A method of preparation of vitamin D<sub>2</sub> is given in Addendum 1936 to the British Pharmacopeia, 1932, p. 20. The crystals have a potency of 40 units of vitamin D (U. S. P.) per microgram. (For methods of assay see U. S. P.)

Vitamin D<sub>2</sub> occurs as a colorless, odorless, acicular, crystalline substance. It is insoluble in water; soluble in alcohol, ether, chloroform, acetone, ethylene glycol and propylene glycol; and sparingly soluble in vegetable oils. The melting point of vitamin D<sub>2</sub> lies between 115° and 118° C. Solutions of vitamin D<sub>2</sub> possess an absorption maximum at 2,640 Å.

Dissolve about 0.5 mg. 8 vitamin D<sub>2</sub> in 5 cc. of chloroform, add 3 drops of acetic anhydride and 3 drops of sulfuric acid and shake the mixture; a bright red color develops which rapidly changes to violet, blue and finally to green.

Dissolve 50 mg. of vitamin D<sub>2</sub> and 0.05 Gm. of 3,5-dinitrobenzoyl chloride in separate 1 cc. portions of anhydrous pyridine. Mix the solutions and warm the mixture on the water bath for ten minutes, add 5 cc. of water, filter and wash the precipitate repeatedly with small amounts of cold water. Recrystallize the precipitated dinitrobenzoyl derivative twice from acetone and finally dry it in a desiccator under partial vacuum: the melting point of the product is from 147° to 149° C. The specific rotation  $[\alpha]_{D/25}$  of the vitamin D<sub>2</sub> dinitrobenzoate dissolved in acetone is + 80°.

Dissolve approximately 10 mg. of vitamin D<sub>2</sub> in 1 cc. of alcohol and add 1 cc. of a 1 per cent solution of digitonin in 90 per cent alcohol; allow the mixture to stand for 12 hours: no precipitate occurs (*absence of ergosterol*).

Dissolve approximately 30 mg. of vitamin D<sub>2</sub>, accurately weighed, in 1 cc. of acetone at 25° C. Put the solution in a 0.5 decimeter tube and measure the optical rotation in a polarimeter at 25° C. using sodium light: the specific rotation lies between + 79.5° and + 83.5°. Determine the amount of carbon and hydrogen present in vitamin D<sub>2</sub> by burning the substance in an appropriate combustion train: the carbon content should not be less than 84.6 per cent nor more than 85.1 per cent; the hydrogen content should not be less than 10.9 per cent nor more than 11.3 per cent.

**VITAMIN K<sub>1</sub>.—C<sub>31</sub>H<sub>46</sub>O<sub>2</sub>.**—M. W. 450.68.—2-Methyl-3-phytyl-1,4-naphthoquinone.

Vitamin K<sub>1</sub> occurs as a yellow, very viscous, nearly odorless liquid of specific gravity about 0.967 and refractive index of 1.5250 at 25° C. It is stable in air but decomposes in sunlight. It is insoluble in water; and soluble in alcohol, benzene, chloroform, ether and vegetable oils.

Suspend one drop of vitamin  $K_1$  in 10 cc. of methanol, add 0.5 cc. six-normal potassium hydroxide in methanol solution and shake. A deep purple color appears immediately, which slowly turns to reddish blue and finally to reddish brown.

Suspend about 0.5 Gm. of vitamin  $K_1$  in 10 cc. of methanol, add a freshly prepared solution of 0.75 Gm. sodium hydrosulfite ( $Na_2S_2O_4$ ) dissolved in 2 cc. of warm water and shake vigorously for a few minutes. The oily vitamin  $K_1$  dissolves and a reddish purple color forms which soon disappears as the mixture becomes colorless. Dilute with water, extract twice with peroxide-free ether and evaporate the ether extract under nitrogen or under vacuum: the white dihydro derivative obtained melts at 88-90° C. This dihydro derivative is readily oxidizable in air. Add one drop of vitamin  $K_1$  to a mixture of 1 cc. of strong ammonia solution and 1 cc. of alcohol and then add one drop of ethylcyanacetate: no purple color is produced (*absence of menadione*). A solution of one part vitamin  $K_1$  and 20 parts alcohol is neutral to litmus.

**ZINC INSULIN CRYSTALS.**—Zinc insulin crystals occur as a crystalline preparation of the active antidiabetic principle of the internal secretion of the islands of Langerhans of the pancreas. The crystals contain a small amount of zinc (not less than 0.45 per cent and not more than 0.9 per cent), which is chemically combined with the active principle. Each milligram of the crystals is equivalent to not less than 22 units of insulin. The product is marketed in the form of crystalline zinc-insulin injection.

Zinc insulin crystals occur as small, colorless crystals which exhibit the following optical properties: uniaxial, positive; habit, flat rhombohedra, with slightly rounded edges, commonly in dual, sometimes in multiple, growths along the C axis, resembling twinning; clear and colorless; elongation of the flat rhombohedra is negative; refractive indices  $\epsilon = 1.556$ ,  $\omega = 1.545$ . It is sparingly soluble in water; insoluble in alcohol, chloroform and ether; but soluble in dilute acid and dilute alkali. The isoelectric point of zinc insulin crystals is about 5.3. The crystals are stable if kept at a low temperature.

Transfer to a microscope slide approximately 0.1 mg. of zinc insulin crystals; add 0.1 cc. of distilled water; thoroughly wet the crystals by stirring with a small glass rod: the crystals do not dissolve completely but give rise to a turbid suspension; examination under the microscope shows the crystals to conform to the petrographic description of zinc insulin crystals. The crystals brown rapidly when heated above 220° C. and melt with decomposition between 230° and 240° C.

Transfer about 20 mg. of zinc insulin crystals to a platinum boat; weigh the boat and its contents within a weighing "pig"; place the boat in a vacuum desiccator over phosphorus pentoxide and dry to constant weight using the weighing "pig" to prevent the absorption of water during weighing. The loss in weight does not exceed 7.0 per cent. In the following quantitative determinations it is more convenient to weigh the zinc insulin crystals directly and to calculate the results to a dry basis rather than attempt to weigh the extremely hygroscopic dry material.

Dissolve 50 mg. of zinc insulin crystals in 5 cc. of water by the addition of sufficient tenth-normal hydrochloric acid to effect solution; transfer to a centrifuge tube and add 2 cc. of 10 per cent trichloroacetic acid with shaking; let stand ten minutes and centrifuge; decant into a 10 cc. volumetric flask, add 2 cc. of Nessler's reagent and make up to volume; allow to stand five minutes; transfer to a colorimeter and compare with a standard made up similarly and containing 0.055 mg. of ammonium sulfate: the color does not exceed that of the standard solution.

Transfer 18 mg. of zinc insulin crystals to a 100 cc. volumetric flask, add 2 cc. of tenth-normal hydrochloric acid, dilute to the mark with distilled water and shake to dissolve the crystals. Transfer 10.0 cc. of this solution to a separatory funnel, add about 20 cc. water, 10 cc. chloro-

form and 2 cc. dithizone reagent (prepared by dissolving 15 mg. dithizone in 100 cc. redistilled chloroform). Make the solution alkaline by the addition of ammonia water and shake until the chloroform layer is colored a clear pink. Drain the chloroform layer into a clean flask and repeatedly extract the aqueous layer with small portions of chloroform to which has been added a few drops of dithizone reagent, until the chloroform is no longer colored pink. At this point the aqueous layer may be discarded. Transfer the combined chloroform extracts to a clean separatory funnel and extract twice with 15 cc. portions of 0.02 normal ammonium hydroxide to remove the excess dithizone. After each extraction, wash the water layer with a small quantity of fresh chloroform and then add it to the main chloroform extract. Dry the combined chloroform extracts with a small quantity of anhydrous, reagent quality, sodium sulfate, decant the solution into a 50 cc. volumetric flask, rinse the sodium sulfate several times with fresh chloroform and make the solution to volume with chloroform. Compare the solution in a colorimeter with a standard made as described above, using 10.0 cc. of a solution containing 0.001 mg. zinc per cubic centimeter (3.357 mg. zinc acetate  $[\text{Zn}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot 2\text{H}_2\text{O}]$  per liter). The zinc content is not less than 0.45 per cent, nor more than 0.9 per cent. (An alternative method for the determination of zinc content is provided in the *U. S. P. XIII*, p. 727, under Zinc in Insulin Injection.)

Transfer about 10 mg. of zinc insulin crystals to a platinum dish; add two drops of concentrated sulfuric acid; ash slowly and ignite to constant weight at 600 C.: the ash is not more than 50 per cent more than the zinc sulfate calculated from the zinc content and in no case is it more than 3.30 per cent.

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# NEW AND NONOFFICIAL REMEDIES

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## SECTION C

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### BIBLIOGRAPHIC INDEX TO MEDICINAL ARTICLES NOT INCLUDED IN N.N.R.

This cumulative index is intended to aid the reader in determining the status of articles which do not stand accepted by the Council and to supply him with sources of useful information on such articles. It provides a ready reference to reports of the Council on Pharmacy and Chemistry explaining the rejection of an article or the omission from New and Non-official Remedies of a previously accepted preparation, to reports of the A. M. A. Chemical Laboratory on unacceptable products, and to critical editorial comments and brief notes in *The Journal of the American Medical Association* pertaining to therapeutic agents not accepted for N. N. R. References to preliminary reports of the Council, which as a rule deal with new articles possessing potential acceptability for N. N. R., are not included. Information on these and on any other article or subject included in the Council's extensive files may be obtained by addressing an inquiry to the Secretary of the Council.

The references given below include: first, the date of original publication of the article in *The Journal A. M. A.*, if it appeared there; and, second, for the benefit of those that do not have access to files of *The Journal*, the place where a discussion of the article may be found in other publications: "Reports of the Council on Pharmacy and Chemistry," "Propaganda for Reform" and "Reports of the A. M. A. Chemical Laboratory." Council reports include reports on articles that have been considered by the Council, either at the request of the manufacturers or on the Council's own initiative. The names of the manufacturers (or their agents) follow the names of the preparations, except in those instances in which a drug is discussed in general, without reference to the product of any particular manufacturer.

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LIQUID CARBONIC CORPORATION, THE, MEDICAL GAS DIVISION, 3100 S. Kedzie Ave., Chicago 23, Ill.—Ethylene, 37.

MACALLISTER LABORATORY, 9213 Wade Park Ave., Cleveland 6, Ohio—Aluminum Hydroxide Gel, 339.

MALLINCKRODT CHEMICAL WORKS, 2nd and Mallinckrodt Sts., St. Louis 7, Mo.—Barbital, 451; Barium Sulfate, 298; Copper Citrate, 215; Hippuran, 302; Iodeikon, 311; Iso-Iodeikon, 315; Mandelic Acid, 122; Mercuric Cyanide, 96; Phenobarbital Sodium, 462; Quinidine, 277; Quinidine Sulfate, 278; Quinine Ethyl Carbonate, 169; Urea, 322; Zinc Peroxide, 117.

MALTBIE CHEMICAL CO., THE, 240-250 High St., Newark 2, N. J.—Ephedrine Sulfate, 232; Sulfanilamide, 138; Sulfathiazole, 142.

MANHATTAN EYE SALVE CO., INC., Louisville, Ky.—Butyn Sulfate, 49; Copper Citrate, 215; Holocaine, 55; Yellow Oxide of Mercury, 97.

MASSENGILL, S. E., COMPANY, Bristol, Tennessee—Aminophylline, 328; Ephedrine Sulfate, 232; Hexestrol, 384.

McKESSON & ROBBINS, INC., Bridgeport 9, Conn.—Ascorbic Acid, 560; Halibut Liver Oil with Viosterol in Oil, 568; Oleo Vitamins A and D, 565; Thiamine Hydrochloride, 550; Viosterol, 563.

MCNEIL LABORATORIES, INC., 2900 N. 17th St., Philadelphia 32, Pa.—Brewer's Yeast, 547; Butisol Sodium, 453; Digitoxin, 268; Dymixal, 79; Menadione, 571; Sulfadiazine, 132; Sulfathiazole, 142.

MEAD JOHNSON & COMPANY, Evansville 21, Ind.—Amigen, 417; Ascorbic Acid, 560; Brewer's Yeast, 547; Cod Liver Oil with Viosterol, 566; Oleum Percomorphum, 569; Protolysate, 417; Sodium Sulfapyrazine, 147; Sulfapyrazine, 140; Viosterol, 563; Viosterol in Halibut Liver Oil, 569.

MEDICAL ARTS LABORATORY, Medical Arts Building, Oklahoma City, Okla.—Rabies Vaccine, 491.

MEDICAL CHEMICALS, 406 E. Water St., Baltimore 2, Md.—Iso-Par, 93.

MERCK & Co., Rahway, N. J.—Agar-Agar, 347; Aminopyrine, 30; Arsphenamine, 179; Barbital, 451; Barbital Sodium, 452; Barium Sulfate, 298; Benzocaine, 46; Betabion, 550; Bismuth Subsalicylate,

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**MERRELL, WM. S., COMPANY, THE, Lockland Station, Cincinnati 15, Ohio**—Aminophylline, 328; Aminopyrine, 30; Ascorbic Acid, 560; Ceepryn Chloride, 72; Dicumarol, 352; Diethylstilbestrol, 380; Diothane Hydrochloride, 51; Ephedrine Sulfate, 233; Hexavitamin, 573; Hexestrol, 384; Menadione Sodium Bisulfite, 573; Methenamine, 123; Nicotinamide, 557; Nicotinic Acid, 555; Penicillin, 155; Phenobarbital Sodium, 461; Riboflavin, 553; Sodium Ascorbate, 562; Soricin Sclerosing, 220; Streptomycin, 162; Sulfadiazine, 132; Sulfanilamide, 138; Sulfathiazole, 143; Thiamine Hydrochloride, 551; Unidigin, 268; Vonedrine, 247.

**MERRELL, WM. S., COMPANY, LOESER LABORATORY DIVISION, Lockland Station, Cincinnati 15, Ohio**—Aminophylline, 328; Hexestrol, 384; Posterior Pituitary, 403; Procaine Hydrochloride, 59.

**MILLER, E. S., LABORATORIES, INC., 743 Maple Ave., Los Angeles 14, Calif.**—Ascorbic Acid, 560; Dehydrocholic Acid, 342; Diethylstilbestrol, 380; Ephedrine Sulfate, 233; Estrogenic Substances, 373; Menadione, 571; Methenamine, 123; Niacinamide, 557; Phenobarbital, 461; Procaine Hydrochloride, 59; Sulfadiazine, 132; Sulfanilamide, 138; Sulfathiazole, 143; Theophylline, 330; Theophylline Ethylenediamine, 328; Thiamine Hydrochloride, 551.

**MILWAUKEE CONVALESCENT SERUM CENTER, Columbia Hospital, Milwaukee 11, Wis.**—Measles Immune Serum (Human), 485; Scarlet Fever Immune Serum (Human), 486.

**MULFORD COLLOID LABORATORIES, 33th and Ludlow Sts., Philadelphia 4, Pa.**—Rhus Tox Antigen, 18; Rhus Venenata Antigen, 19.

**NATIONAL ANILINE DIVISION, ALLIED CHEMICAL AND DYE CORPORATION, 40 Rector St., New York, 6, N. Y.**—Acridine, 78; Acridine Hydrochloride, 78; Gentian Violet, 82; Phenolsulfonphthalein, 313; Proflavine, 79; Scarlet Red, 75; Scarlet Red Sulfonate, 75; Succinchlorimide, 90.

**NATIONAL DRUG CO., THE, 4664-85 Stenton Ave., Philadelphia 44, Pa.**—Allergenic Extracts, 14; Ascorbic Acid, 560; Diphtheria and Tetanus Toxoids, Alum Precipitated, 499; Diphtheria-Tetanus-Pertussis Combined Vaccine, 503; Diphtheria Toxin for Schick Test, 513; Diphtheria Toxinoid, 496; Diphtheria Toxinoid, Alum Precipitated, 498; Diphtheria Toxinoid, Alum Precipitated and Pertussis Vaccine Combined, 508; Ephedrine Sulfate, 233; Gas Gangrene Antitoxin, 480; Mannitol Hexanitrate, 275; Nicotinic Acid, 555; Nikethamide, 282; Pertussis Vaccine, 505; Pertussis Vaccine, Alum Precipitated, 506; Rabies Vaccine, 491; Scarlet Fever Streptococcus Toxin, 493; Scarlet Fever Streptococcus Toxin for the Dick Test, 514; Sodium Morrhuate, 219; Staphylococcus Toxinoid, 500; Staphylococcus Toxinoid-Vaccine, 512; Sulfanilamide, 138; Tetanus-Gas Gangrene Antitoxin, 481; Tetanus Toxinoid, Alum Precipitated, 502; Thiamine Hydrochloride, 551; Typhoid Vaccine, 511; Undulant Fever Vaccine, 504.



NEW YORK QUININE AND CHEMICAL WORKS, INC., 99-117 N. 11th St., Brooklyn, N. Y.—Nicotinic Acid, 555.

NOVOCOL CHEMICAL MFG. CO., INC., 2911-23 Atlantic Ave., Brooklyn 7, N. Y.—Amylsine Hydrochloride, 47; Monocaine Formate, 53; Monocaine Hydrochloride, 54.

OHIO CHEMICAL & MFG. CO., THE, 2633 Fourth Ave., South, Minneapolis 8, Minn.—Cyclopropane, 36; Ethylene Gas, 37.

ORTHO PHARMACEUTICAL CORPORATION, Linden, N. J.—Hexestrol, 385; Ortho-Creme, 289; Ortho-Gynol Vaginal Jelly, 290; Ortho Vaginal Applicator, 290.

PARKE, DAVIS & COMPANY, Detroit 23, Mich.—Adrenalin, 235; Adrenalin Chloride 1:100, 241; Adrenalin Chloride 1:1,000, 238; Adrenalin in Oil 1:500, 240; Allergenic Extracts, Diagnostic, 7; Ascorbic Acid, 560; Benadryl Hydrochloride, 21; Bismuth Paste Surgical, 95; Bismuth Salicylate, 198; Chloretone, 439; Cod Liver Oil with Viosterol, 566; Dilantin Sodium, 440; Diphtheria-Tetanus Toxoid, 499; Diphtheria Toxin for Schick Test, 513; Diphtheria Toxoid, 497; Diphtheria Toxoid, Alum Precipitated, 498; Diphtheria Toxoid-Pertussis Vaccine, 508; Ephedrine Hydrochloride, 231; Ephedrine Sulfate, 233; Ergot Aseptic, 337; Furunculosis Vaccine, 510; Gas Gangrene Antitoxin, 480; Haliver Oil with Viosterol, 569; Mapharsen, 183; Neo-Silvol, 112; Nicotinic Acid, 555; Ortol Sodium, 457; Paroidin, 399; Penicillin, 155; Pertussis Vaccine, 505; Pertussis Vaccine, Alum Precipitated, 506; Phemerol Chloride, 73; Pitocin, 401; Pitressin, 402; Pitressin Tannate, 403; Pituitrin, 404; Poison Ivy Extract, 18; Potassio-Mercuric Iodide, 97; Sal-Ethyl, 33; Sal-Ethyl Carbonate, 33; Scarlet Fever Streptococcus Antitoxin, 483; Scarlet Fever Streptococcus Toxin, 494; Scarlet Fever Streptococcus Toxin for the Dick Test, 514; Scarlet Red, 75; Silver Nitrate, 113; Silvol, 112; Staphylococcus Toxoid, 501; Sulfadiazine, 132; Sulfamerazine, 135; Sulfanilamide, 138; Sulfathiazole, 143; Tetanus-Gas Gangrene Antitoxin, 482; Tetanus Toxoid, Alum Precipitated, 502; Theelin, 370; Theelol, 369; Thio-Bismol, 200; Thrombin Topical, 358; Tuberculin for the Mantoux Test, 519; Tuberculin Old, 519; Tuberculin Old for the von Pirquet Test, 519; Tuberculin, Purified Protein Derivative, 517; Typhoid Vaccine, 511; Tyrothricin, 67; Ventriculin, 361; Viosterol, 564.

PATCH, E. L., THE, Stoneham Post Office, Boston, Mass.—Kondremul, 348.

PENNSYLVANIA SALT MFG. COMPANY, 1000 Widener Building, Philadelphia 7, Pa.—Hyclorite, 89.

PERNOX, INCORPORATED, 330 W. 42nd St., New York, N. Y.—Pernox Vaginal Capsules, 291.

PFIZER, CHAS. & COMPANY, INC., 11 Bartlett St., Brooklyn 6, N. Y.—Penicillin, 156; Streptomycin, 162.

PHARMEDIC CORPORATION, 160 E. 127th St., New York, N. Y.—Aminophylline, 328.

PHILADELPHIA SERUM EXCHANGE, The Children's Hospital, 1740 Bainbridge St., Philadelphia 46, Pa.—Pertussis Immune Serum (Human), 487.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC., Indianapolis 6, Ind.—Allergenic Extracts, 14; Anti-Erysipeloid Serum, 484; Ascorbic Acid, 560; Diphtheria-Tetanus Toxoid, Alum Precipitated, 499; Diphtheria Toxin for the Schick Test, 513; Diphtheria Toxoid, Alum Precipitated, 498; Ephedrine Hydrochloride, 231; Influenza Virus Vaccine, Types A and B, 489; Nicotinic Acid, 555; Poison Ivy Extract, 18; Poison Oak Extract, 19; Rabies Vaccine (Ultraviolet Irradiation Killed), 493; Siomine, 423; Staphylococcus

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**PREMO PHARMACEUTICAL LABORATORIES, INC.**,—443 Broadway, New York 13, N. Y.—Aminophylline, 328; Ascorbic Acid, 560; Chiniofon, 202; Diethylstilbestrol, 80; Digitoxin, 268; Diphenylhydantoin Sodium, 440; Ephedrine Sulfate, 233; Merbromin, 99; Nikethamide, 282; Penicillin, 156; Pentobarbital Sodium, 459; Riboflavin, 553; Streptomycin, 162; Sulfathiazole, 143; Triasyn B, 552; Vitamin A, 545.

**PURITAN COMPRESSED GAS CORPORATION**, 2012 Grand Ave., Kansas City 8, Mo.—Ethylene, 37.

**RARE CHEMICALS, INC.**, First and Essex Sts., Harrison, N. J.—Dienestrol, 377; Gitalin, 271; Methyltestosterone, 410; Salysal, 32; Testosterone Propionate, 411.

**RAYMER PHARMACAL COMPANY**, N. E. Corner Jasper & Willard Sts., Philadelphia 34, Pa.—Aminophylline, 329.

**REED & CARRICK**, 155 Van Wagenan Ave., Jersey City, New Jersey—Estrogenic Substances, 373.

**THE RESERVE RESEARCH Co.**, 222 Phoenix Building, Cleveland, Ohio—Aluminum Hydroxide Gel, 339.

**RORER, WM. H., INC.**, 254 S. 4th St., Philadelphia 6, Pa.—Aluminum Hydroxide Gel, 339; Aminophylline, 329; Carfusin, 82; Diethylstilbestrol, 381; Ephedrine Sulfate, 233; Mannitol Hexanitrate, 275; Sodium Ascorbate, 562; Sulfadiazine, 132; Thiamine Hydrochloride, 551.

**SANDOZ CHEMICAL WORKS, INC.**, 68-70 Charlton St., New York 14, N. Y.—Digilanid, 266; Gynergen, 337; Sandoptal, 448; Scillaren, 273; Scillaren-B, 273.

**SARGENT'S DRUG STORE, INC.**, 23 N. Wabash Ave., Chicago 2, Ill.—Petrobran, 349.

**SCHENLEY LABORATORIES, INC.**, 350 Fifth Ave., New York 1, N. Y.—Penicillin, 157.

**SCHERING CORPORATION**, 2 Broad St., Bloomfield, N. J.—Estinyl, 384; Neo-Iopax, 309; Priodax, 303.

**SCHERING & GLATZ, INC.**, 113 W. 18th St., New York, N. Y.—Euphthalmine Hydrochloride, 258; Iocampen, 90; Medinal, 452; Urotropin, 123; Xeroform, 95.

**SCHIEFFELIN & Co.**, 16-30 Cooper Square, New York 3, N. Y.—Aluminum Hydroxide Gel, 339; Ascorbic Acid, 560; Benzetrol, 377; Sulfanilamide, 138; Sulfathiazole, 143; Thiamine Hydrochloride, 551.

**SCHMID JULIUS, INC.**, 423 W. 55th St., New York 19, N. Y.—Ramses Vaginal Applicator, 290; Ramses Vaginal Jelly, 290.

**SEARLE, G. D. & Co.**, Post Office Box 5110, Chicago 80, Ill.—Aminophyllin, 329; Bismuth Sodium Tartrate, 195; Diodoquin, 203; Gold Sodium Thiosulfate, 525; Metamucil, 350; Sodium Morrhuate, 219.

**SEYDEL CHEMICAL COMPANY**, 225 Mercer St., Jersey City 2, N. J.—Benzyl Alcohol, 48.

**SHARPE & DOHME, INC.**, Glenolden, Pa.—Antivenin (Latrodectus mactans), 478; Blood Group Specific Substances A and B, 472; Chorionic Gonadotropin, 408; Cremo-Bismuth, 347; Cresatin Metacresylacetate (Sulzberger), 68; Delvinal Sodium, 467; Digitol, 269; Diphtheria-

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**SMITH, CARROLL DUNHAM, PHARMACAL Co.,** New Brunswick, N. J.—Aminophylline, 329; Ascorbic Acid, 561; Bistramate, 196; Calcium Levulinate, 421; Diethylstilbestrol, 381; Estrusol, 374; Nikethamide, 282; Penicillin, 157; Sodium Dehydrocholate, 346; Sulfadiazine, 132; Sulfanilamide, 138; Sulfathiazole, 143; Thiamine Hydrochloride, 551.

**SMITH-DORSEY COMPANY,** Lincoln, Nebr.—Aminophylline, 329; Ascorbic Acid, 561; Bismuth Subsalcylate, 198; Diethylstilbestrol, 381; Ephedrine Sulfate, 233; Epinephrine in Oil, 1:500, 240; Estrogenic Substances, 374; Liquid Petrolatum, 348; Mannitol Hexanitrate, 275; Menadione, 571; Nicotinic Acid, 555; Nikethamide, 282; Penicillin, 157; Phenobarbital, 461; Pyridoxine Hydrochloride, 558; Sulfadiazine, 132; Sulfanilamide, 139; Sulfathiazole, 143; Thiamine Hydrochloride, 551.

**SMITH, KLINE & FRENCH, Laboratories,** 5th and Arch Sts., Philadelphia 5, Pa.—Benzedrine, 225; Benzedrine Sulfate, 227.

**SMITH OIL & REFINING Co.,** Rockford, Ill.—Mineral Oil, 348.

**SMITH, UPSHER, Co.,** 529 So. Seventh St., Minneapolis, Minn.—Pyrethrum, 118.

**SPECIAL FORMULA CORPORATION,** 445 Park Ave., New York 22, N. Y.—Lygel Vaginal Applicator, 289; Lygel Vaginal Cream, 289; Lygel Vaginal Jelly, 289.

**SQUIBB, E. R., & SONS,** 745 Fifth Ave., New York 22, N. Y.—Amniotin, 375; Ascorbic Acid, 561; Brewer's Yeast, 548; Chlorarsen, 180; Cod Liver Oil with Viosterol, 566; Cyclopropane, 36; Diethylstilbestrol, 381; Diphtheria and Tetanus Toxoid Alum Precipitated and Pertussis Vaccine Combined, 509; Diphtheria Toxin for the Schick Test, 513; Diphtheria Toxoid, 497; Diphtheria Toxoid, Alum Precipitated, 498; Diphtheria Toxoid-Tetanus Toxoid, Alum Precipitated, 500; Follutein, 408; Gas Gangrene Antitoxin, 480; Globin Insulin with Zinc, 390; Influenza Virus Vaccine, Types A and B, 489; Insulin, 393; Intocostrin, 211; Iodobismutol, 199; Ipral Calcium, 463; Ipral Sodium, 464; Mannitol Hexanitrate, 276; Mineral Oil, 348; Neoarsphenamine, 182; Penicillin, 158; Pertussis Vaccine, 505; Posterior Pituitary, 404; Procaine Hydrochloride, 59; Protamine Zinc Insulin, 396; Rabies Vaccine (Semple), 492; Scarlet Fever Streptococcus Toxin, 494; Scarlet Fever Streptococcus Toxin for the Dick Test, 514; Sodium Sulfadiazine Sterile, 146; Streptomycin, 163; Sulfadiazine, 132; Sulfaguanidine, 134; Sulfamerazine, 135; Sulfathiazole, 143; Tetanus Gas Gangrene Antitoxin, 482; Tetanus Toxoid, Alum Precipitated, 503; Thiamine Hydrochloride, 551; Thyloquinone, 571; Viosterol, 564.

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- THOMPSON, MARVIN R., INC.**, 67 Greenwich Ave., Stamford, Conn.—Vitamin B complex, 548.
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- U. S. STANDARD PRODUCTS Co.**, Wadsworth, Wis.—Allergenic Extracts, 15; Diphtheria Toxoid, 497; Diphtheria Toxoid, Alum Precipitated, 498; Epinephrine Hydrochloride 1:1,000, 238; Posterior Pituitary, 404; Procaine Hydrochloride, 60; Rabies Vaccine (Semple), 492; Scarlet Fever Streptococcus Toxin, 494; Scarlet Fever Streptococcus Toxin for the Dick Test, 514; Tetanus Gas Gangrene Antitoxin, 482; Typhoid Vaccine, 511.
- U. S. VITAMIN CORPORATION**, 250 East 43rd St., New York 17, New York—Ascorbic Acid, 561; Menadione, 572; Niacin, 555; Niacinamide, 557; Pyridoxine Hydrochloride, 558; Riboflavin, 554; Thiamine Hydrochloride, 551.
- UPJOHN COMPANY, THE**, Kalamazoo 99, Mich.—Adrenal Cortex, 365; Aluminum Hydroxide Gel, 340; Ascorbic Acid, 561; Bismuth Ethylcamphorate, 194; Bismuth Subsalicylate, 198; Carbromal, 437; Diethylstilbestrol, 381; Ephedrine Sulfate, 233; Epinephrine, 236; Epinephrine Hydrochloride 1:1,000, 238; Gelfoam, 430; Heparin Sodium, 353; Mercresin, 100; Nicotinic Acid, 555; Nicotinic Acid Amide, 557; Nikethamide, 282; Penicillin, 158; Pertussis Vaccine, 506; Pertussis Vaccine, Alum Precipitated, 506; Pertussis Vaccine, Diphtheria Toxoid, 508; Phenobarbital, 461; Posterior Pituitary, 404; Procaine Hydrochloride, 59; Pyridoxine Hydrochloride, 558; Racephedrine Hydrochloride, 247; Riboflavin, 554; Sodium Morrhuate, 219; Streptomycin, 163; Sulfadiazine, 132; Sulfamerazine, 135; Sulfanilamide, 139; Sulfathiazole, 143; Thiamine Hydrochloride, 552.
- VALE CHEMICAL Co., INC., THE**, 814-816 Gordon St., Allentown, Pa.—Aminophylline, 330; Diethylstilbestrol, 381; Menadione, 572; Nicotinamide, 557; Phenobarbital, 461; Sulfadiazine, 132; Sulfathiazole, 143; Thiamine Hydrochloride, 552.
- VARICK PHARMACAL Co., INC.**, 75 Varick St., New York 13, N. Y.—Digitaline Nativele, 268.
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- WALKER VITAMIN PRODUCTS, INC.**, Mount Vernon, N. Y.—Ascorbic Acid, 561; Hexavitamin, 574; Niacinamide, 557; Nicotinic Acid, 555; Oleo Vitamin A, 545; Oleo Vitamin A-D, 565; Riboflavin, 554; Thiamine Hydrochloride, 552; Vitamin C Drops, 561.
- WALLACE & TIERNAN PRODUCTS, INC.**, Belleville 9, N. J.—Azochloramid, 87; Monomestrol, 385; Sodium Sotradecol, 221.
- WARNER, WILLIAM R., & Co., INC.**, 113 W. 18th St., New York 11, N. Y.—Nikethamide, 282; Penicillin, 159.
- WARREN-TEED PRODUCTS COMPANY**, 582 W. Goodale St., Columbus 8, Ohio—Aminophylline, 330; Ascorbic Acid, 561; Diethylstilbestrol, 381; Ephedrine Hydrochloride, 231; Epinephrine Hydrochloride 1:1,000, 238; Estrovarin, 375; Niacin, 555; Nicotinamide, 557; Phenobarbital, 461; Phenobarbital Sodium, 461; Posterior Pituitary, 404; Riboflavin, 554; Sulfanilamide, 139; Sulfathiazole, 143; Thiamine Hydrochloride, 552; Aristol, 92; Ascorbic Acid, 561; Atabrine di-Hydrochloride, 167; Avertin with Amylene Hydrate, 39; Bile Salts, 345; Chiniofon, 202; Creamalin, 340; Demerol Hydrochloride, 27; Dichlorophenarsine Hydrochloride, 181; Diethylstilbestrol, 381; Diethylstilbestrol Dipropionate, 382; Diodrast, 307; Diodrast Com-

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WILSON LABORATORIES, DIVISION OF WILSON & CO., INC., 4221 S. Western Ave., Chicago 9, Ill.—Epinephrine, 236; Epinephrine Hydrochloride 1:1,000, 239; Gastric Mucin, 347; Posterior Pituitary, 404.

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